Charles M. Lizza
William C. Baton
SAUL EWING ARNSTEIN & LEHR LLP
One Riverfront Plaza, Suite 1520
Newark, NJ 07102-5426
(973) 286-6700
clizza@saul.com

OF COUNSEL:

Raymond N. Nimrod
Colleen Tracy James
Catherine T. Mattes
QUINN EMANUEL URQUHART & SULLIVAN, LLP
51 Madison Avenue
New York, NY 10010

Attorneys for Plaintiffs
Mitsubishi Tanabe Pharma Corp.,
Janssen Pharmaceuticals, Inc., Janssen Pharmaceutica NV,
Janssen Research and Development, LLC,
and Cilag GmbH International

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

MITSUBISHI TANABE PHARMA CORPORATION, JANSSEN PHARMACEUTICALS, INC., JANSSEN PHARMACEUTICA NV, JANSSEN RESEARCH AND DEVELOPMENT, LLC, and CILAG GMBH INTERNATIONAL,

Plaintiffs,

v.

AUROBINDO PHARMA USA, INC.,

Defendant.

Civil Action No. _____

COMPLAINT FOR PATENT INFRINGEMENT

(Filed Electronically)

Plaintiffs Mitsubishi Tanabe Pharma Corp. ("MTPC"), Janssen Pharmaceuticals, Inc. ("JPI"), Janssen Pharmaceutica NV ("JNV"), Janssen Research and Development, LLC ("JRD"), and Cilag GmbH International ("Cilag") (collectively, "Plaintiffs"), by their attorneys, for their complaint against Aurobindo Pharma USA, Inc. ("Aurobindo"), allege as follows:

NATURE OF THE ACTION

1. This is a civil action for infringement of United States Patent Nos. 7,943,582 (the "'582 patent") and 8,513,202 (the "'202 patent") (collectively, the "Patents-in-Suit") under the patent laws of the United States, 35 U.S.C. §100, *et seq.* This action arises from Aurobindo's filing of Abbreviated New Drug Application ("ANDA") No. 213900 ("the Aurobindo ANDA") with the United States Food and Drug Administration ("FDA") seeking approval to commercially market generic versions of JPI's canagliflozin and metformin hydrochloride extended-release tablets, 50 mg/1000 mg and 150 mg/1000 mg INVOKAMET XR® drug product ("the Aurobindo ANDA Products") prior to the expiration of the Patents-in-Suit.

THE PARTIES

2. MTPC is a corporation organized and existing under the laws of Japan, having an office and place of business at 3-2-10, Dosho-machi, Chuo-ku, Osaka 541-8505, Japan.

3. JPI is a corporation organized and existing under the laws of the State of Pennsylvania, having its principal place of business at 1125 Trenton-Harbourton Road, Titusville, New Jersey 08560.

4. JNV is a corporation organized and existing under the laws of Belgium, having its principal place of business at Turnhoutseweg, 30, 2340 Beerse, Belgium.

5. JRD is a corporation organized and existing under the laws of the State of New Jersey, having its principal place of business at 920 Route 202, Raritan, New Jersey 08869.

6. Cilag is a company organized and existing under the laws of Switzerland, having its principal place of business at Gubelstrasse 34, 6300, Zug, Switzerland.

7. On information and belief, defendant Aurobindo is a corporation organized and existing under the laws of the State of Delaware, having its principal place of business at 279 Princeton Hightstown Rd., East Windsor, New Jersey 08520.

THE PATENTS-IN-SUIT

8. On May 17, 2011, the United States Patent and Trademark Office ("USPTO") duly and lawfully issued the '582 patent, entitled, "Crystalline form of 1-(β-D-glucopyransoyl)-4-methyl-3-[5-(4-fluorophenyl)-2- thienylmethyl]benzene hemihydrate" to MTPC as assignee of inventors Sumihiro Nomura and Eiji Kawanishi. A copy of the '582 patent is attached as Exhibit A.

9. JPI, JRD, and Cilag are exclusive licensees of the '582 patent.

10. JNV is an exclusive sublicensee of the '582 patent.

11. On August 20, 2013, the USPTO duly and lawfully issued the '202 patent, entitled, "Crystalline form of 1-(β-D-glucopyransoyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene hemihydrate" to MTPC as assignee of inventors Sumihiro Nomura and Eiji Kawanishi. A copy of the '202 patent is attached as Exhibit B.

12. JPI, JRD, and Cilag are exclusive licensees of the '202 patent.

13. JNV is an exclusive sublicensee of the '202 patent.

THE INVOKAMET XR® DRUG PRODUCT

14. JPI holds approved New Drug Application ("NDA") No. 205879 for extended release canagliflozin and metformin hydrochloride tablets, which are prescribed and

sold under the trademark INVOKAMET XR®. INVOKAMET XR® is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

15. The claims of the Patents-in-Suit cover, *inter alia*, certain polymorphic forms of canagliflozin.

16. Pursuant to 21 U.S.C. § 355(b)(1), and attendant FDA regulations, the '582 and '202 patents are listed in the FDA publication, "Approved Drug Products with Therapeutic Equivalence Evaluations" (the "Orange Book"), with respect to INVOKAMET XR®.

SUBJECT MATTER JURISDICTION

17. This action arises under the patent laws of the United States, 35 U.S.C. §§ 100, *et seq*., and this Court has jurisdiction over the subject matter of this action under 28 U.S.C. §§ 1331, 1338(a), 2201, and 2202.

PERSONAL JURISDICTION AND VENUE OVER AUROBINDO

18. This Court has personal jurisdiction over Aurobindo because, *inter alia*, Aurobindo has committed an act of patent infringement under 35 U.S.C. § 271(e)(2) and intends a future course of conduct that includes acts of patent infringement in New Jersey. These acts have led and will lead to foreseeable harm and injury to Plaintiffs in New Jersey. For example, on information and belief, following approval of the Aurobindo ANDA, Aurobindo will make, use, offer for sale, sell, and/or import the Aurobindo ANDA Products in the United States, including in New Jersey, prior to the expiration of the Patents-in-suit.

19. This Court also has personal jurisdiction over Aurobindo because, *inter alia*, this action arises from actions of Aurobindo directed toward New Jersey. For example, Aurobindo's counsel sent a letter dated February 7, 2020 to JPI, a corporation with its principal place of business in this Judicial District stating that Aurobindo had submitted ANDA No. 213900 seeking approval to commercially manufacture, use, import, offer for sale, and sell the

Aurobindo ANDA Products prior to the expiration of the Patents-in-Suit. If Aurobindo succeeds in obtaining FDA approval, it would sell its Aurobindo ANDA Products in New Jersey and other states, causing injury to Plaintiffs in New Jersey.

20. The Court also has personal jurisdiction over Aurobindo because Aurobindo has purposefully availed itself of the rights and benefits of New Jersey law by engaging in systematic and continuous contacts with the State of New Jersey. On information and belief, Aurobindo regularly and continuously transacts business within New Jersey, including by maintaining its principal place of business in New Jersey and by selling pharmaceutical products in New Jersey. On information and belief, Aurobindo derives substantial revenue from the sale of those products in New Jersey and has availed itself of the privilege of conducting business within New Jersey.

21. On information and belief, Aurobindo has continuously placed its products into the stream of commerce for distribution and consumption in the State of New Jersey and throughout the United States, and thus has engaged in the regular conduct of business within this Judicial District.

22. On information and belief, Aurobindo derives substantial revenue from selling generic pharmaceutical products throughout the United States, including in this Judicial District.

23. On information and belief, Aurobindo has previously invoked, stipulated, and/or consented to personal jurisdiction in this Judicial District in numerous prior patent cases.

24. Aurobindo has previously been sued in this Judicial District and has availed itself of New Jersey courts through the assertion of counterclaims in suits brought in New Jersey, including *Mitsubishi Tanabe Pharma Corp., et al. v. Aurobindo Pharma Ltd., et al.*,

Civil Action No. 17-5005 (D.N.J.) (not contesting personal jurisdiction or venue and asserting counterclaims); *Mitsubishi Tanabe Pharma Corp., et al. v. Aurobindo Pharma Ltd., et al.*, Civil Action No. 17-5319 (not contesting personal jurisdiction or venue and asserting counterclaims); *Shionogi & Co., Ltd., et al. v. Aurobindo Pharma Ltd., et al.*, Civil Action No. 15-0319 (D.N.J.) (not contesting personal jurisdiction or venue and asserting counterclaims); *Takeda Pharmaceutical Company Ltd., et al. v. Aurobindo Pharma Ltd., et al.*, Civil Action No. 15-7635 (D.N.J) (not contesting personal jurisdiction or venue and asserting counterclaims); and *Astrazeneca Pharmaceuticals LP, et al. v. Aurobindo Pharma Limited, Inc., et al.*, Civil Action No. 07-6020 (D.N.J.) (admitting to personal jurisdiction and venue and asserting counterclaims).

25. Venue is proper for Aurobindo under 28 U.S.C. § 1400(b) because Aurobindo has a regular and established place of business in New Jersey, and has or will commit acts of infringement in New Jersey, as set forth in paragraphs 18-24.

AUROBINDO'S INFRINGING ANDA SUBMISSION

26. On or about February 10, 2020, JPI received from Aurobindo's counsel a letter, dated February 7, 2020 ("Aurobindo February 7 Letter"), stating that Aurobindo had submitted the Aurobindo ANDA to the FDA seeking approval to market the Aurobindo ANDA Products before the expiration of the Patents-in-Suit. MTPC received the Aurobindo February 7 Letter on or about February 11, 2020.

27. Aurobindo specifically directed the Aurobindo February 7 Letter to JPI's headquarters in Raritan, New Jersey, within this Judicial District.

28. The Aurobindo ANDA Products are intended to be generic versions of INVOKAMET XR®.

29. The Aurobindo February 7 Letter alleges that the Aurobindo ANDA Products do not infringe the '582 patent or the '202 patent. Notwithstanding these allegations, on information and belief, discovery/testing will show that the Aurobindo ANDA Products infringe the Patents-in-Suit.

30. This action is being commenced before the expiration of 45 days from the date MTPC and JPI received the Aurobindo February 7 Letter.

COUNT I
Infringement of U.S. Patent No. 7,943,582 by Aurobindo

31. Plaintiffs repeat and reallege paragraphs 1-30 above as if fully set forth herein.

32. On information and belief, Aurobindo submitted or caused the submission of ANDA No. 213900 to the FDA, and thereby seeks FDA approval of Aurobindo's ANDA Products.

33. Plaintiffs own all rights, title, and interest in and to the '582 Patent.

34. By filing its ANDA No. 213900 for the purpose of obtaining approval to engage in the commercial manufacture, use, offer for sale, sale, and/or importation into the United States of the Aurobindo ANDA Products before the expiration of the '582 patent, Aurobindo committed an act of infringement under 35 U.S.C. § 271(e)(2).

35. If Aurobindo commercially makes, uses, offers to sell, or sells the Aurobindo ANDA Products within the United States, or imports the Aurobindo ANDA Products into the United States, or induces or contributes to any such conduct during the term of the '582 patent, it would further infringe at least claims 1, 6, and 7 of the '582 patent under 35 U.S.C. §§ 271(a), (b), and/or (c).

36. Aurobindo has had knowledge of the ’582 patent since at least the date it submitted the Aurobindo ANDA.

37. Plaintiffs will be irreparably harmed if Aurobindo is not enjoined from infringing the ’582 patent. Plaintiffs do not have an adequate remedy at law, and considering the balance of hardships between Plaintiffs and Aurobindo, a remedy in equity is warranted. Further, the public interests would not be disserved by the entry of a permanent injunction.

COUNT II
Infringement of U.S. Patent No. 8,513,202 by Aurobindo

38. Plaintiffs repeat and reallege paragraphs 1-37 above as if fully set forth herein.

39. On information and belief, Aurobindo submitted or caused the submission of ANDA No. 213900 to the FDA, and thereby seeks FDA approval of Aurobindo’s ANDA Products.

40. Plaintiffs own all rights, title, and interest in and to the ’202 Patent.

41. By filing its ANDA No. 213900 for the purpose of obtaining approval to engage in the commercial manufacture, use, offer for sale, sale, and/or importation into the United States of the Aurobindo ANDA Products before the expiration of the ’202 patent, Aurobindo committed an act of infringement under 35 U.S.C. § 271(e)(2).

42. If Aurobindo commercially makes, uses, offers to sell, or sells the Aurobindo ANDA Products within the United States, or imports the Aurobindo ANDA Products into the United States, or induces or contributes to any such conduct during the term of the ’202 patent, it would further infringe at least claims 1 and 3-5 of the ’202 patent under 35 U.S.C. §§ 271(a), (b), and/or (c).

43. Aurobindo has had knowledge of the ’202 patent since at least the date Aurobindo submitted the Aurobindo ANDA.

44. Plaintiffs will be irreparably harmed if Aurobindo is not enjoined from infringing the ’202 patent. Plaintiffs do not have an adequate remedy at law, and considering the balance of hardships between Plaintiffs and Aurobindo, a remedy in equity is warranted. Further, the public interests would not be disserved by the entry of a permanent injunction.

PRAYER FOR RELIEF

WHEREFORE, Plaintiffs respectfully request the following relief:

A. A Judgment that Aurobindo has infringed one or more claims of the ’582 patent by filing ANDA No. 213900;

B. A Judgment that Aurobindo has infringed, and that Aurobindo’s making, using, offering to sell, selling, or importing the Aurobindo ANDA Products would constitute infringement of one or more claims of the ’582 patent, and/or induce or contribute to the infringement of one or more claims of the ’582 patent pursuant to 35 U.S.C. §§ 271(a), (b) and/or (c);

C. A permanent injunction restraining and enjoining Aurobindo, and its officers, agents, attorneys, and employees, and those acting in privity or concert with them, from engaging in the commercial manufacture, use, offer for sale, or sale within the United States, or importation into the United States, of the Aurobindo ANDA Products until after the expiration of the ’582 patent, or any later expiration of exclusivity to which Plaintiffs are or become entitled;

D. An Order that the effective date of any approval of ANDA No. 213900 relating to the Aurobindo ANDA Products be a date that is not earlier than the expiration date of

the ’582 patent as extended plus any other regulatory exclusivity to which Plaintiffs are or become entitled;

E. A Judgment that Aurobindo has infringed one or more claims of the ’202 patent by filing ANDA No. 213900;

F. A Judgment that Aurobindo has infringed, and that Aurobindo’s making, using, offering to sell, selling, or importing the Aurobindo ANDA Products would constitute infringement of one or more claims of the ’202 patent, and/or induce or contribute to the infringement of one or more claims of the ’202 patent pursuant to 35 U.S.C. § 271(a), (b) and/or (c);

G. A permanent injunction restraining and enjoining Aurobindo, and its officers, agents, attorneys, and employees, and those acting in privity or concert with them, from engaging in the commercial manufacture, use, offer for sale, or sale within the United States, or importation into the United States, of the Aurobindo ANDA Products until after the expiration of the ’202 patent, or any later expiration of exclusivity to which Plaintiffs are or become entitled;

H. An Order that the effective date of any approval of ANDA No. 213900 relating to the Aurobindo ANDA Products be a date that is not earlier than the expiration date of the ’202 patent as extended plus any other regulatory exclusivity to which Plaintiffs are or become entitled;

I. An award of damages or other relief, pursuant to 35 U.S.C. § 271(e)(4)(C), if Aurobindo engages in the commercial manufacture, use, offer for sale, sale, and/or importation of its ANDA Product, or any product that infringes the ’582 or ’202 Patents, or induces or contributes to such conduct, prior to the expiration of those patents including any additional exclusivity period applicable to those patents; and

J. Such other and further relief as the Court may deem just and proper.

Dated: March 20, 2020

By: s/ Charles M. Lizza

Charles M. Lizza
William C. Baton
SAUL EWING ARNSTEIN & LEHR LLP
One Riverfront Plaza, Suite 1520
Newark, NJ 07102-5426
(973) 286-6700
clizza@saul.com

Attorneys for Plaintiffs Mitsubishi Tanabe Pharma Corp., Janssen Pharmaceuticals, Inc. Janssen Pharmaceutica NV, Janssen Research and Development, LLC, and Cilag GmbH International

OF COUNSEL:

Raymond N. Nimrod
Colleen Tracy James
Catherine T. Mattes
QUINN EMANUEL
URQUHART & SULLIVAN, LLP
51 Madison Avenue
New York, NY 10010

CERTIFICATION PURSUANT TO LOCAL CIVIL RULES 11.2 & 40.1

I hereby certify that the matters captioned *Mitsubishi Tanabe Pharma Corporation, et al. v. Aurobindo Pharma USA, Inc., et al.*, Civil Action No. 17-5005 (RMB)(JS) (consolidated), *Mitsubishi Tanabe Pharma Corporation, et al. v. Prinston Pharmaceutical Inc., et al.*, Civil Action No. 17-5135 (RMB)(JS), *Mitsubishi Tanabe Pharma Corporation, et al. v. Apotex, Inc., et al.*, Civil Action No. 17-5278 (RMB)(JS), *Mitsubishi Tanabe Pharma Corporation, et al. v. MSN Laboratories Private Ltd., et al.*, Civil Action No. 17-5302 (PGS)(DEA), *Mitsubishi Tanabe Pharma Corporation, et al. v. Prinston Pharmaceuticals, Inc.*, Civil Action No. 17-7342 (FLW)(DEA), *Mitsubishi Tanabe Pharma Corporation, et al. v. Macleods Pharmaceuticals, Ltd., et al.*, Civil Action No. 17-13130 (RMB)(JS), *Mitsubishi Tanabe Pharma Corporation, et al. v. Lupin Ltd., et al.*, Civil Action No. 18-292 (RMB)(JS), and *Mitsubishi Tanabe Pharma Corporation, et al. v. Lupin Ltd., et al.*, Civil Action No. 19-7165 (RMB)(JS), and *Mitsubishi Tanabe Pharma Corporation, et al. v. MSN Laboratories Private Ltd., et al.*, Civil Action No. 19-15616 (RMB)(JS) are related to the matter in controversy because the matter in controversy involves one of the same patents.

I hereby certify that, to the best of my knowledge, the matter in controversy is not the subject of any other action pending in any court or of any pending arbitration or administrative proceeding.

Dated: March 20, 2020

By: s/ Charles M. Lizza

Charles M. Lizza
William C. Baton
SAUL EWING ARNSTEIN & LEHR LLP
One Riverfront Plaza, Suite 1520
Newark, NJ 07102-5426
(973) 286-6700
clizza@saul.com

Attorneys for Plaintiffs Mitsubishi Tanabe Pharma Corp., Janssen Pharmaceuticals, Inc. Janssen Pharmaceutica NV, Janssen Research and Development, LLC, and Cilag GmbH International

OF COUNSEL:

Raymond N. Nimrod
Colleen Tracy James
Catherine T. Mattes
QUINN EMANUEL
URQUHART & SULLIVAN, LLP
51 Madison Avenue
New York, NY 10010

EXHIBIT A

US007943582B2

(12) **United States Patent**
Nomura et al.

(10) **Patent No.: US 7,943,582 B2**
(45) **Date of Patent: May 17, 2011**

(54) **CRYSTALLINE FORM OF 1-(β-D-GLUCOPYRANSOYL)-4-METHYL-3-[5-(4-FLUOROPHENYL)-2-THIENYLMETHYL]BENZENE HEMIHYDRATE**

(75) Inventors: **Sumihiro Nomura**, Osaka (JP); **Eiji Kawanishi**, Osaka (JP)

(73) Assignee: **Mitsubishi Tanabe Pharma Corporation**, Osaka-Shi (JP)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 451 days.

(21) Appl. No.: **11/987,670**

(22) Filed: **Dec. 3, 2007**

(65) **Prior Publication Data**

US 2008/0146515 A1 Jun. 19, 2008

Related U.S. Application Data

(60) Provisional application No. 60/868,426, filed on Dec. 4, 2006.

(30) **Foreign Application Priority Data**

Dec. 4, 2006 (JP) 2006-327019

(51) **Int. Cl.**
A61K 31/7034 (2006.01)
C07H 7/04 (2006.01)

(52) **U.S. Cl.** **514/23**; 536/1.11

(58) **Field of Classification Search** ..... None
See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

4,160,861	A	7/1979	Cole et al.
4,584,369	A	4/1986	Klein et al.
5,149,838	A	9/1992	Humphrey et al.
5,424,406	A	6/1995	Tsujihara et al.
5,731,292	A	3/1998	Tsujihara et al.
5,767,094	A	6/1998	Tsujihara et al.
5,780,483	A	7/1998	Widdowson et al.
5,830,873	A	11/1998	Tsujihara et al.
6,048,842	A	4/2000	Tsujihara et al.
6,153,632	A	11/2000	Rieveley
6,297,363	B1	10/2001	Kubo et al.
6,414,126	B1	7/2002	Ellsworth et al.
6,515,117	B2	2/2003	Ellsworth et al.
6,562,791	B1	5/2003	Maurya et al.
6,617,313	B1	9/2003	Maurya et al.
6,627,611	B2	9/2003	Tomiyama et al.

(Continued)

FOREIGN PATENT DOCUMENTS

CA	2494177	A1	2/2004

(Continued)

OTHER PUBLICATIONS

Ahmad et al., "Synthesis and Structure Determination of Some Oxadiazole-2-Thione and Triazole-3-Thione Galactosides", Nucleosides, Nucleotides & Nucleic Acids, vol. 20, No. 9, 2001, pp. 1671-1682.

(Continued)

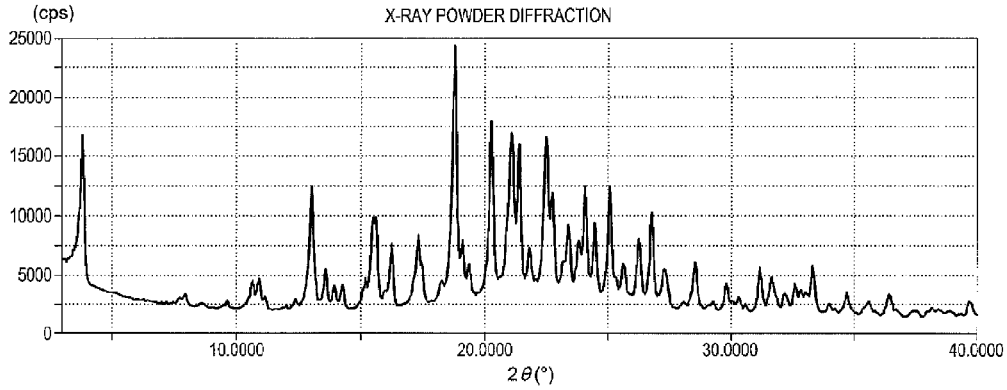
Primary Examiner — Eric S Olson

(74) *Attorney, Agent, or Firm* — Birch, Stewart, Kolasch & Birch, LLP

(57) **ABSTRACT**

A novel crystal form of 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene hemihydrate, and having favorable characteristics, is characterized by its x-ray powder diffraction pattern and/or by its infra-red spectrum.

7 Claims, 2 Drawing Sheets



U.S. PATENT DOCUMENTS

7,375,213	B2	5/2008	Deshpande et al.	
7,511,022	B2	3/2009	Beavers et al.	
2001/0041674	A1	11/2001	Tomiyama et al.	
2002/0032164	A1	3/2002	Dale et al.	
2002/0052326	A1	5/2002	Washburn	
2002/0111315	A1	8/2002	Washburn et al.	
2003/0024914	A1	2/2003	Aleshin	
2003/0064935	A1	4/2003	Gougoutas	
2003/0087843	A1	5/2003	Washburn	
2003/0114390	A1	6/2003	Washburn et al.	
2004/0053855	A1	3/2004	Fujikura et al.	
2004/0063646	A1	4/2004	Fujikura et al.	
2004/0110936	A1	6/2004	Ohsumi et al.	
2004/0116357	A1	6/2004	Fushimi et al.	
2004/0132669	A1	7/2004	Nishimura et al.	
2004/0138143	A1	7/2004	Glombik et al.	
2004/0259819	A1	12/2004	Frick et al.	
2005/0014704	A1	1/2005	Frick et al.	
2005/0032711	A1	2/2005	Patel et al.	
2005/0032712	A1	2/2005	Urbanski	
2005/0037980	A1	2/2005	Rybczynski et al.	
2005/0037981	A1	2/2005	Beavers et al.	
2005/0124556	A1	6/2005	Burton	
2005/0233988	A1*	10/2005	Nomura et al.	514/43
2006/0217323	A1	9/2006	Patel et al.	
2006/0229260	A1	10/2006	Rybczynski et al.	
2006/0234954	A1	10/2006	Urbanski	
2006/0293251	A1	12/2006	Urbanski et al.	
2007/0060545	A1	3/2007	Nomura et al.	

FOREIGN PATENT DOCUMENTS

EP	0355750	A1	2/1990
EP	0579204	A3	1/1994
EP	1338603	A1	8/2003
EP	1528066	A1	5/2005
GB	2359554	A	8/2001
JP	63-233975	A	9/1988
JP	4-253974	A	9/1992
JP	9-263549	A	10/1997
JP	10-324632	A	12/1998
JP	2000-34230	A	2/2000
JP	2000-34239	A	2/2000
JP	2001-288178	A	10/2001
JP	2003-12686	A	1/2003
WO	WO 93/21178	A1	10/1993
WO	WO 97/25033	A1	7/1997
WO	WO 00/74681	A1	12/2000
WO	WO 01/27128	A1	4/2001
WO	WO 01/64669	A1	9/2001
WO	WO 01/68660	A1	9/2001
WO	WO 01/74834	A1	10/2001
WO	WO 01/74835	A1	10/2001
WO	WO 02/053573	A1	7/2002
WO	WO 02/068439	A1	9/2002
WO	WO 02/068440	A1	9/2002
WO	WO 02/070020	A2	9/2002
WO	WO 02/083066	A2	10/2002
WO	WO 02/088157	A1	11/2002
WO	WO 02/094262	A1	11/2002
WO	WO 03/000712	A1	1/2003
WO	WO 03/011880	A1	2/2003
WO	WO 03/020737	A1	3/2003
WO	WO 03/043621	A1	5/2003
WO	WO 03/087104	A1	10/2003
WO	WO 03/099836	A1	12/2003
WO	WO 2004/007517	A	1/2004
WO	WO 2004/013118	A	2/2004
WO	WO 2004/014931	A1	2/2004
WO	WO 2004/018442	A1	3/2004
WO	WO 2004/019958	A1	3/2004
WO	WO 2004/052902	A1	6/2004
WO	WO 2004/052903	A1	6/2004
WO	WO 2004/063209	A2	7/2004
WO	WO 2004/080990	A1	9/2004
WO	WO 2004/087727	A1	10/2004
WO	WO 2004/099230	A1	11/2004
WO	WO 2004/113359	A1	12/2004
WO	WO-2005/012326	A1	2/2005
WO	WO 2005/030127	A2	4/2005
WO	WO 2006/108842	A1	10/2006
WO	WO 2006/120208	A1	11/2006
WO	WO 2007/035198	A2	3/2007
WO	WO 2007/054978	A2	5/2007
WO	WO 2007/107354	A1	9/2007

OTHER PUBLICATIONS

Appleton et al, "A Mild and Selective C-3 Reductive Alkylation of Indoles", Tetrahedron Letters, vol. 34, No. 9, 1993, pp. 1529-1532.

Arakawa et al, "Improved diabetic syndrome in C57BL/KsJ-db/db mice by oral administration of the Na+ -glucose cotransporter inhibitor T-1095," British Journal of Pharmacology, vol. 132, 2001, pp. 578-586.

Banker et al. (Editors), Modern Pharmaceutics, Third Edition, published 1996, p. 596, Marcel Dekker, Inc.

Benhaddou et al.,"Tetra-n-propylammonium tetraoxoruthenate(VII): a reagent of choice for the oxidation of diversely protected glycopyranoses and glycofuranoses to lactones", Carbohydrate Research, vol. 260, 1994, pp. 243-250.

Bertolini et al., "A New Simple One-Pot Regioselective Preparation of Mixed Diesters of Carbonic Acid.", Journal of Organic Chemistry, vol. 63, No. 17, 1998, pp. 6031-6034.

Blair et al., "Effect of Ring Fluorination on the Pharmacology of Hallucinogenic Tryptamines", J. Med. Chem., vol. 43, 2000, pp. 4701-4710.

Boehm et al., "Novel Inhibitors of DNA Gyrase: 3D Structure Based Biased Needle Screening, Hit Validation by Biophysical Methods, and 3D Guided Optimization. A Promising Alternative to Random Screening," J. Med. Chem., vol. 43, No. 14, 2000, pp. 2664-2674.

Brooks et al., "Boron Trichloride/Tetra-n-Butylammonium Iodide: A Mild, Selective Combination Reagent for the Cleavage of Primary Alkyl Aryl Ethers", J. Org. Chem., vol. 64, 1999, pp. 9719-9721.

CAS Reg. No. 487001-40-1, IPOrganisers, Entered STN Feb. 7, 2003, pp. 1-2.

Comins et al., "Synthesis of 3-Substituted Indoles Via N-Acylindolium Ions", Tetrahedron Letters, vol. 27, No. 17, 1986, pp. 1869-1872.

Czernecki et al., "C-Glycosides. 7. Stereospecific C-Glycosylation of Aromatic and Heterocyclic Rings", J. Org. Chem., vol. 54, 1989, pp. 610-612.

Deeg et al., "Pioglitazone and Rosiglitazone Have Different Effects on Serum Lipoprotein Particle Concentrations and Sizes in Patients With Type 2 Diabetes and Dyslipidemia.", Diabetes Care, vol. 30, No. 10, Oct. 2007, pp. 2458-2464.

Deetjen et al., "Renal Handling of D-Glucose and Other Sugars", Textbook of Nephrology, vol. 1, 3rd Edition, 1995, pp. 90-94.

Devivar et al., "Benzimidazole Ribonucleosides: Design, Synthesis, and Antiviral Activity of Certain 2-(Alkylthio)- and 2-(Benzylthio)-5,6-dichloro-1-(β-D-ribofuranosyl)benzimidazoles1," J.Med. Chem., vol. 37, 1994, pp. 2942-2949.

Dewynter et al., "Synthesis of Pseudonucleosides containing Chiral Sulfahydantoins as Aglycone (II)", Tetrahedron, vol. 52, No. 3, 1996, pp. 993-1004.

Dillard et al., "Indole Inhibitors of Human Nonpancreatic Secretory Phospholipase A2. 1. Indole-3-acetamides", J. Med. Chem., vol. 39, 1996, pp. 5119-5136.

Dondoni et al., "Stereoselective synthesis of C-glycosylphosphonates from their ketols. Reconsideration of an abandoned route", Tetrahedron: Asymmetry, vol. 11, 2000, pp. 305-317.

Dondoni et al., "Thiazole-Based Synthesis of Formyl C-Glycosides", J. Org. Chem., vol. 59, 1994, pp. 6404-6412.

Dudash, Jr. et al, "Glycosylated dihydrochalcones as potent and selective sodium glucose co-transporter 2 (SGLT2) inhibitors," Bioorganic & Medicinal Chemistry Letters, vol. 14, 2004, pp. 5121-5125.

Dunn et al., "Analgetic and antiinflammatory 7-Aroylbenzofuran-5-ylacetic acids and 7-Aroylbenzothiophene-5-ylacetic Acids.", Journal of Med. Chem., vol. 29, No. 1, 1986, pp. 2326-2329.

Eid et al., "Reaction of Some 1,2,4-Triazines with Acetobromoglucose", Arch. Pharm. (Weinheim), vol. 323, 1990, pp. 243-245.
Ellsworth et al, "Aglycone exploration of C-arylglucoside inhibitors of renal sodium-dependent glucose transporter SGLT2," Bioorganic & Medicinal Chemistry Letters, vol. 18, 2008, pp. 4770-4773.
Ellsworth et al., "C-Arylglucoside synthesis: triisopropylsilane as a selective reagent for the reduction of an anomeric C-phenyl ketal," Tetrahedron: Asymmetry, vol. 14, 2003, pp. 3243-3247.
Fresneda et al., "Synthesis of the indole alkaloids meridianins from the tunicate Aplidium meridianum," Tetrahedron, vol. 57, 2001, pp. 2355-2363.
Gershell, "Type 2 diabetes market", Nature Reviews Drug Discovery, vol. 4, May 2005, pp. 367-368.
Goodman & Gilman's The Pharmacological Basis of Therapeutics, 10th Edition, McGraw-Hill Medical Publishing Division, 2001, pp. 54-57.
Han et al., "Dapagliflozin, a Selective SGLT2 Inhibitor, Improves Glucose Homeostasis in Normal and Diabetic Rats", Diabetes, vol. 57, Jun. 2008, pp. 1723-1729.
Handlon, "Sodium glucose co-transporter 2 (SGLT2) inhibitors as potential antidiabetic agents," Expert Opin. Ther. Patents, vol. 15, No. 11, 2005, pp. 1531-1540.
Hofslokken et al., "Convenient Method for the ortho-Formylation of Phenols.", Acta Chemica Scandinavica, vol. 53, 1999, pp. 258-262.
Hongu et al., "Na+-Glucose Cotransporter Inhibitors as Antidiabetic Agents. II.1) Synthesis and Structure-Activity Relationships of 4'-Dehydroxyphlorizin Derivatives", Chem. Pharm. Bull., vol. 46, No. 1, 1998, pp. 22-33.
Horton et al., "Synthetic Routes to Higher-Carbon Sugars. Reaction of Lactones with 2-Lithio-1,3-Dithiane", Carbohydrate Research, vol. 94, 1981, pp. 27-41.
Hu et al., "A New Approach Towards the Yellowing Inhibition of Mechanical Pulps. Part I: Selective Removal of alpha-Hydroxyl and alpha-Carbonyl Groups in Lignin Model Compounds", Holzforschung, vol. 53, No. 1, 1999, pp. 43-48.
Huang-Minlon, "Reduction of Steroid Ketones and other Carbonyl Compounds by Modified Wolff-Kishner Method", J. Am. Chem. Soc., vol. 71, Oct. 1949, pp. 3301-3303.
Ibrahim et al., "Selective Synthesis and Structure of 2-N- and 3-S-Glucosyl-1,2,4-Triazoles of Potential Biological Interest", Carbohydrate Letters, vol. 3, No. 5, 1999, pp. 331-338.
Ibrahim, "Facile Approach for the Selective Glycosidation of Cyclic Asymmetric Amides and Thioamides", Carbohydrate Letters, vol. 1, 1996, pp. 425-432.
Information Submission of Sep. 1, 2009 in U.S. Appl. No. 11/045,446, including Appendices A, B and C.
International Search Report for Application No. PCT/JP2004/011312, dated Nov. 25, 2004.
Isaji, "Sodium-glucose cotransporter inhibitor for diabetes," Current Opinion in Investigational Drugs, vol. 8, No. 4, 2007, pp. 285-292.
Kahn et al, "Normalization of Blood Glucose in Diabetic Rats with Phlorizin Treatment Reverses Insulin-resistant Glucose Transport in Adipose Cells without Restoring Glucose Transporter Gene Expression," J. Clin. Invest., vol. 87, Feb. 1991, pp. 561-570.
Kanai et al., "The Human Kidney Low Affinity Na+/Glucose Cotransporter SGLT2: Delineation of the Major Renal Reabsorptive Mechanism for D-Glucose", J. Clin. Invest., vol. 93, Jan. 1994, pp. 397-404.
Kasahara et al., "A missense mutation in the Na+/glucose cotransporter gene SGLT1 in a patient with congenital glucose-galactose malabsorption: normal trafficking but inactivation of the mutant protein," Biochimica et Biophysica Acta, vol. 1536, 2001, pp. 141-147.
Katz et al., "Quantitative Insulin Sensitivity Check Index: A Simple, Accurate Method for Assessing Insulin Sensitivity In Humans.", J. of Clin. Endrocrinology & Metabolism, vol. 85, No. 7, 2000, pp. 2402-2410.
Ketcha et al., "Synthesis of Alyl-Substituted N-Protected Indoles via Acylation and Reductive Deoxygenation1" J. Org. Chem., vol. 54, 1989, pp. 4350-4356.
Khan et al, "Reactions of Phenyl-Substituted Heterocyclic Compounds—II. Nitrations and Brominations of 1-Phenylpyrazole Derivatives," Canadian Journal of Chemistry, vol. 41, 1963, pp. 1540-1547.
Liang et al., "JNJ-28431754/TA-7284, an Inhibitor of Sodium-Glucose Cotransporter 2, Ameliorates Diabetic Syndrome in the Zucker Diabetic Fatty Rat," Oct. 2009, Poster presented at International Diabetes Federation 20th World Diabetes Congress, Montreal, Canada.
Liang et al., "JNJ-28431754/TA-7284, an Inhibitor of Sodium-Glucose Cotransporter 2, Reduces Body Weight Gain in Zucker Fatty Rats," Oct. 2009, Poster presented at International Diabetes Federation 20th World Diabetes Congress, Montreal, Canada.
Liang et al., "JNJ-28431754/TA-7284, an SGLT Inhibitor, Lowers Blood Glucose and Reduces Body Weight in Obese and type 2 Diabetic Animal Models," Jun. 2009.
Lin et al., "Syntheses of Guanidinoglycosides with the Inventive use of Mitsunobu Conditions and 1, 8-Diazabicyclo[5.4.0]undec-7-ene.", Synthesis, No. 2, 2003, pp. 255-261.
Link et al., "A method for preparing C-glycosides related to phlorizin" Tetrahedron Letters, vol. 41, 2000, pp. 9213-9217.
Lipscombe et al., "Trends in diabetes prevalence, incidence, and mortality in Ontario, Canada 1995-2005: a population-based study", Lancet, vol. 369, 2007, pp. 750-756.
Maatooq, "C-p-Hydroxybenzoylglycoflavones from Citrullus Colocynthis", Phytochemistry, vol. 44, No. 1, Jan. 1997, pp. 187-190.
Mackenzie et al., "Biophysical Characteristics of the Pig Kidney Na+/Glucose Cotransporter SGLT2 Reveal a Common Mechanism for SGLT1 and SGLT2", J. Biol. Chem., vol. 271, No. 5, 1996, pp. 32678-32683.
Manis et al., "Metabolism of 4,4'-Methylenebis(2-chloroaniline) By Canine Liver and Kidney Slices.", Drug Metabolism and Disposition, vol. 14, No. 2, 1986, pp. 166-174.
Marsenic, "Glucose Control by the Kidney: An Emerging Target in Diabetes.", Am. J. of Kidney Diseases, vol. 53, No. 5, May 2009, pp. 875-883.
Matsuda et al., "Insulin Sensitivity Indices Obtained From Oral Glucose Tolerance Testing: Comparison with the euglycemic insulin clamp," Diabetes Care, vol. 22, No. 9, Sep. 1999, pp. 1462-1470.
Matthews et al., "Homeostasis model assessment: insulin resistance and β-cell function from fasting plasma glucose and insulin concentrations in man," Diabetolgia, vol. 28, 1985, pp. 412-419.
Meanwell et al., "Regiospecific Functionalization of 1,3-Dihydro-2H-benzimidazol-2-one and Structurally Related Cyclic Urea Derivates.", J. Org. Chemistry, vol. 60, No. 6, 1995, pp. 1565-1582.
Meng et al., "Discovery of Dapagliflozin: A Potent, Selective Renal Sodium-Dependent Glucose Cotransporter 2 (SGLT2) Inhibitor for the Treatment of Type 2 Diabetes", J. Med. Chem., vol. 51, No. 5, 2008, pp. 1145-1149.
Mewshaw et al., "New Generation Dopaminergic Agents. 7. Heterocyclic Bioisosteres that Exploit the 3-OH-Phenoxyethylamine D2 Template", Bioorganic & Medicinal Chemistry Letters, vol. 9, 1999, pp. 2593-2598.
Miyaura et al., "Palladium-Catalyzed Cross-Coupling Reactions of Organoboron Compounds.", Chem. Rev., vol. 95, No. 7, 1995, pp. 2457-2483.
Nishimura et al, "Tissue-specific mRNA Expression Profiles of Human ATP-binding Cassette and Solute Carrier Transporter Superfamilies," Drug Metab. Pharmacokinet., vol. 20, No. 6, 2005, pp. 452-477.
Nomura et al., "Discovery of Novel C-glucosides with Thiophene Ring as Sodium-dependent Glucose Cotransporter 2 Inhibitors for the Treatment of Type 2 Diabetes Mellitus", MEDI 151, Abstract, The 238th ACS National Meeting, Washington, DC, Aug. 16-20, 2009; American Chemical Society: Washington, DC.
Nomura, "Renal Sodium-Dependent Glucose Cotransporter 2 (SGLT2) Inhibitors for New Anti-Diabetic Agent," Current Topics in Medicinal Chemistry, vol. 10, No. 4, 2010, pp. 411-418.
Office Action in U.S. Appl. No. 11/045,446, dated Dec. 5, 2008.
Office Action in U.S. Appl. No. 11/045,446, dated Jun. 16, 2008.
Office Action in U.S. Appl. No. 11/045,446, dated Oct. 1, 2009.

Ohsumi et al. "Pyrazole-O-Glucosides as Novel Na+-Glucose Cotransporter (SGLT) Inhibitors" Bioorganic & Medicinal Chemistry Letters, vol. 13, 2003, pp. 2269-2272.
Oku et al., "T-1095, an Inhibitor of Renal Na+-Glucose Cotransporters, May Provide a Novel Approach to Treating Diabetes", Diabetes, vol. 48, Sep. 1999, pp. 1794-1800.
Orjales et al. "New 2-Piperazinylbenzimidazole Derivatives as 5-HT-3 Antagonists. Synthesis and Pharmacological Evaluation," J. Med. Chem., vol. 40, 1997, pp. 586-593.
Patani et al., "Bioisosterism: A Rational Approach to Drug Design", Chem. Rev., American Chemical Society, vol. 96, 1996, pp. 3147-3176.
Peng et al., "Post-transcriptional Regulaton of Na+/Glucose Cotransporter (SGTL1) Gene Expression in LLC-PK1 Cells.", Journal of Biological Chemistry, vol. 270, No. 35, 1995, pp. 20536-20542.
Polidori et al., "Frequently Used Insulin Sensitivity Measures May Be Inappropriate for Subjects Treated With SGLT2 Inhibitors," Jun. 2009, Poster presented at the American Diabetes Assoc. 69th Scientific Sessions, Jun. 5-9, 2009, New Orleans, LA.
Raynaud et al., "Revised Concept for the Estimation of Insulin Sensitivity From a Single Sample.", Diabetes Care, vol. 22, No. 6, Jun. 1999, pp. 1003-1004.
Rossetti et al, "Correction of Hyperglycemia with Phlorizin Normalizes Tissue Sensitivity to Insulin in Diabetic Rats," J. Clin. Invest., vol. 79, May 1987, pp. 1510-1515.
Rossetti et al, "Effect of Chronic Hyperglycemia on in Vivo Insulin Secretion in Partially Pancreatectomized Rats," J. Clin. Invest., vol. 80, Oct. 1987, pp. 1037-1044.
Rossetti et al., "Glucose Toxicity," Diabetes Care, vol. 13, Issue 6, 1990, pp. 610-630, Abstract only.
Silverman, "The Organic Chemistry of Drug Design and Drug Action," Academic Press, 1992, pp. 19-23.
Somei et al., "The First and Simple Total Synthesis of Capparilosides A1," Heterocycles, vol. 53, No. 7, 2000, pp. 1573-1578.
Srogl et al., "Sulfonium Salts. Participants par Excellence in Metal-Catalyzed Carbon-Carbon Bond-Forming Reactions", J. Am. Chem. Soc., vol. 119, No. 50, 1997, pp. 12376-12377.
Stoner et al, "Benzylation via Tandem Grignard Reaction—Iodotrimethylsilane (TMSI) Mediated Reduction," Tetrahedron, vol. 51, No. 41, 1995, pp. 11043-11062.
Stumvoll et at "Use of the Oral Glucose Tolerance Test to Assess Insulin Release and Insulin Sensitivity.", Diabetes Care, vol. 23, No. 3, Mar. 2000, pp. 295-301.
Tanaka et al. "Solid-Phase Synthesis of β-Mono-Substituted Ketones and an Application to the Synthesis of a Library of Phlorizin Derivatives", Synlett, No. 9, 2002, pp. 1427-1430.
The State Intellectual Property Office of P.R. China Office Action, Appl. No. 2004800220078, Dec. 26, 2008, pp. 1-6, Second Office Action, English translation.
The State Intellectual Property Office of P.R. China Office Action, Appl. No. 2004800220078, Oct. 19, 2007, pp. 1-6, First Office Action, English translation.
The State Intellectual Property Office of P.R. China The Decision of Rejection (PCT) Action, Appl. No. 2004800220078, Nov. 2009, pp. 1-7.
The State Intellectual Property Office of P.R. China, Observations (1st), Appl. No. 2004800220078, May 2008, pp. 1-3, English translation.
The State Intellectual Property Office of P.R. China, Observations (2nd), Appl. No. 2004800220078, May 2009, pp. 1-4, English translation.
The State Intellectual Property Office of P.R. China, Record of Interview, Appl. No. 2004800220078, Sep. 2009, pp. 1-7, English translation.
The State Intellectual Property Office of P.R. China, Response to The Decision of Rejection (PCT), Appl. No. 2004800220078, Feb. 2010, pp. 1-27, English translation.
Thornber, "Isosterism and Molecular Modification in Drug Design", Chemical Society Reviews, vol. 8, 1979, pp. 563-580.
Tsujihara et al, "Na+-Glucose Cotransporter (SGLT) Inhibitors as Antidiabetic Agents. 4. Synthesis and Pharmacological Properties of 4'-Dehydroxyphlorizin Derivatives Substituted on the B Ring," J. Med. Chem., vol. 42, No. 26, 1999, pp. 5311-5324.
Tsujihara et al., "Na+-Glucose Cotransporter Inhibitors as Antidiabetic.I. Synthesis and Pharmacological Properties of 4'-Dehydroxyphlorizin Derivatives Based on a New Concept," Chem. Pharm. Bull., vol. 44, No. 6, 1996, pp. 1174-1180.
Tsujihara et al., Bio Clinica, vol. 13, No. 4, 1998, pp. 324-328, English language Abstract.
Turk et al., "Glucose/galactose malabsorption caused by a defect in the Na+/glucose cotransporter," Nature, vol. 350, Mar. 1991, pp. 354-356.
Ueta et al, "Anti-diabetic and Anti-obesity effects of TA-7284, a Novel SGLT2 Inhibitor," Partial English translation, JDS Poster Presentation, 2009.
Ueta et al, "Long-term treatment with the Na+-glucose cotransporter inhibitor T-1095 causes sustained improvement in hyperglycemia and prevents diabetic neuropathy in Goto-Kakizaki Rats," Life Sciences, vol. 76, 2005, pp. 2655-2668.
Unger et al., "Hyperglycaemia as an inducer as well as a consequence of impaired islet cell function and insulin resistance: implications for the management of diabetes.", Diabetologia, vol. 28, 1985, pp. 119-121.
Wallace et al., "Use and Abuse of HOMA Modeling.", Diabetes Care, vol. 27, No. 6, Jun. 2004, pp. 1487-1495.
Wang et al, "Selective monolithiation of 2,5-dibromopyridine with butyllithium," Tetrahedron Letters, vol. 41, 2000, pp. 4335-4338.
Wareham et al., "Is There Really an epidemic of diabetes?", Diabetologia, vol. 48, 2005, pp. 1454-1455.
Washburn, "Evolution of sodium glucose co-transporter 2 inhibitors as anti-diabetic agents," Expert Opin. Ther. Patents, vol. 19, No. 11, 2009, pp. 1485-1499.
Wild et al., "Global Prevalence of Diabetes: Estimates for the year 2000 and projections for 2030," Diabetes Care, vol. 27, No. 5, May 2004, pp. 1047-1053.
Wolff, vol. 1: Principles and Practice, Burger's Medicinal Chemistry and Drug Discovery, 5th Edition, 1995, pp. 975-977.
Wright, "Renal Na+-glucose cotransporters," Am J Physiol Renal Physiol, vol. 280, 2001, pp. F10-F18.
Yang et al., "Convergent C-Glycolipid Synthesis via the Ramberg-Bäcklund Reaction: Active Antiproliferative Glycolipids", vol. 1, No. 13, Org. Lett. 1999, pp. 2149-2151.
Zamani, "Synthesis and Structure Determination of Some New N-Glycosides of 4,5-Disubstituted-1,2,4-triazole-3-thiones", Journal of the Chinese Chemical Society, vol. 49, 2002, pp. 1041-1044.
Zhou, "The Synthesis and Characterization of 1-Benzyl-3-N-(Beta-D-glucoside-1-yl)-5-fluorouracil", Hecheng Huaxue, vol. 9, No. 3, 2001, pp. 272-274.
Amishiro, N. et al., "Synthesis and Antitumor Activity of Duocarmycin Derivatives: A-Ring Pyrrole Compounds Bearing 5-Membered Heteroarylacryloyl Groups," Chem. Pharm. Bull., Oct. 1999, vol. 47, No. 10, pp. 1393-1403.
Bookser, B.C., "2-Benzyloxymethyl-5-(tributylstannyl)tetrazole. A reagent for the preparation of 5-aryl- and 5-heteroaryl-1H-tetrazoles via the Stille reaction," Tetrahedron Letters, 2000, vol. 41, pp. 2805-2809.
Bouillon, A. et al, "Synthesis of novel halopyridinylboronic acids and esters. Part 2: 2,4, or 5-Halopyridin-3-yl-boronic acids and esters," Tetrahedron, 2002, vol. 58, pp. 3323-3328.
Bouillon, A. et al, "Synthesis of novel halopyridinylboronic acids and esters. Part 3: 2, or 3-Halopyridin-4-yl-boronic acids and esters," Tetrahedron, 2002, vol. 58, pp. 4369-4373.
Bouillon, A. et al, "Synthesis of novel halopyridinylboronic acids and esters. Part 4: Halopyridin-2-yl-boronic acids and esters are stable, crystalline partners for classical Suzuki cross-coupling," Tetrahedron, 2003, vol. 59, pp. 10043-10049.
Cicchillo, R.M. et al, "A convenient synthesis of glycosyl chlorides from sugar hemiacetals using triphosgene as the chlorine source," Carbohydrate Research, 2000, vol. 328, pp. 431-434.
Clayden, J. et al, "Dearomatizing Cyclization of Arylsulfonylalkoxymethyl Lithiums: A Route to the Podophyllotoxin Skeleton," Organic Letters, 2003, vol. 5, No. 6, pp. 831-834.

Cottet, F. et al, "Recommendable Routes to Trifluoromethyl-Substituted Pyridine- and Quinolinecarboxylic Acids," Eur. J. Org. Chem., 2003, pp. 1559-1568.
De Las Heras, F. G. et al, "Alkylating Nucleosides 1. Synthesis and Cytostatic Activity of N-Glycosyl(halomethyl)-1,2,3-triazoles. A New Type of Alkylating Agent," Journal of Medicinal Chemistry, 1979, vol. 22, No. 5, pp. 496-501.
Frahn, J. et al, "Functionalized AB-Type Monomers for Suzuki Polycondensation," Synthesis, Nov. 1997, pp. 1301-1304.
Fuller, L.S. et al, "Thienothiophenes. Part 2. Synthesis, metallation and bromine-lithium exchange reactions of thieno[3,2-b-thiophene and its polybromo derivatives," J. Chem. Soc., Perkin Trans. 1., 1997, pp. 3465-3470.
Ganesh, T. et al, "Synthesis and biological evaluation of fluorescently labeled epothilone analogs for tubulin binding studies," Tetrahedron, 2003, vol. 59, pp. 9979-9984.
Gohier, F. et al, "ortho-Metalation of Unprotected 3-Bromo and 3-Chlorobenzoic Acids with Hindered Lithium Dialkylamides," J. Org. Chem., 2003, vol. 68, pp. 2030-2033.
Gronowitz, S. et al, "Some Substitution Reactions of 1-(2-Thienyl)pyrazole and 1-(3'-Thienyl)pyrazole," Chemica Scripta., 1979, vol. 13, pp. 157-161.
Gros, P. et al, "Efficient and Regioselective Access to Bis-heterocycles via Palladium-Catalysed Coupling of Organostannanes and Organozincates Derived from C-6 Lithiated 2-Methoxypyridine," Synthesis, 1999, No. 5, pp. 754-756.
Lee, J. S. et al, "Synthesis and In Vitro Activity of Novel Isoxazolyl Tetrahydropyridinyl Oxazolidinone Antibacterial Agents," Bioorganic & Medicinal Chemistry Letters, 2003, vol. 13, pp. 4117-4120.
Messaoudi, S. et al, "Synthesis and biological evaluation of oxindoles and benzimidazolinones derivatives," European Journal of Medicinal Chemistry, 2004, vol. 39, pp. 453-458.
Parker, K. A. et al, "Reductive Aromatization of Quinols: Synthesis of the C-Arylglycoside Nucleus of the Paulacandins and Chaetiacandin," Organic Letters, 2000, vol. 2, No. 4, pp. 497-499.
Schmidt, R. R. et al, "Synthese von Pyrazol-, Pyrazolo[3,4-d]pyrimidin-und 1H-1,2,4-Triazolgluconucleosiden aus Glucosehydrazonen," Liebigs Ann. Chem., 1981, pp. 2309-2317.
Tilak, B.D. et al, "Carcinogenesis by Thiophene Isosters of Polycyclic Hydrocarbons," Tetrahedron, 1960, vol. 9, pp. 76-95.
Yoshimura, H. et al, "Discovery of Novel and Potent Retinoic Acid Receptor alpha-Agonists: Synthesis and Evaluation of Benzofuranyl-pyrrole and Benzothiophenyl-pyrrole Derivatives," J. Med. Chem., 2000, vol. 43, pp. 2929-2937.

* cited by examiner

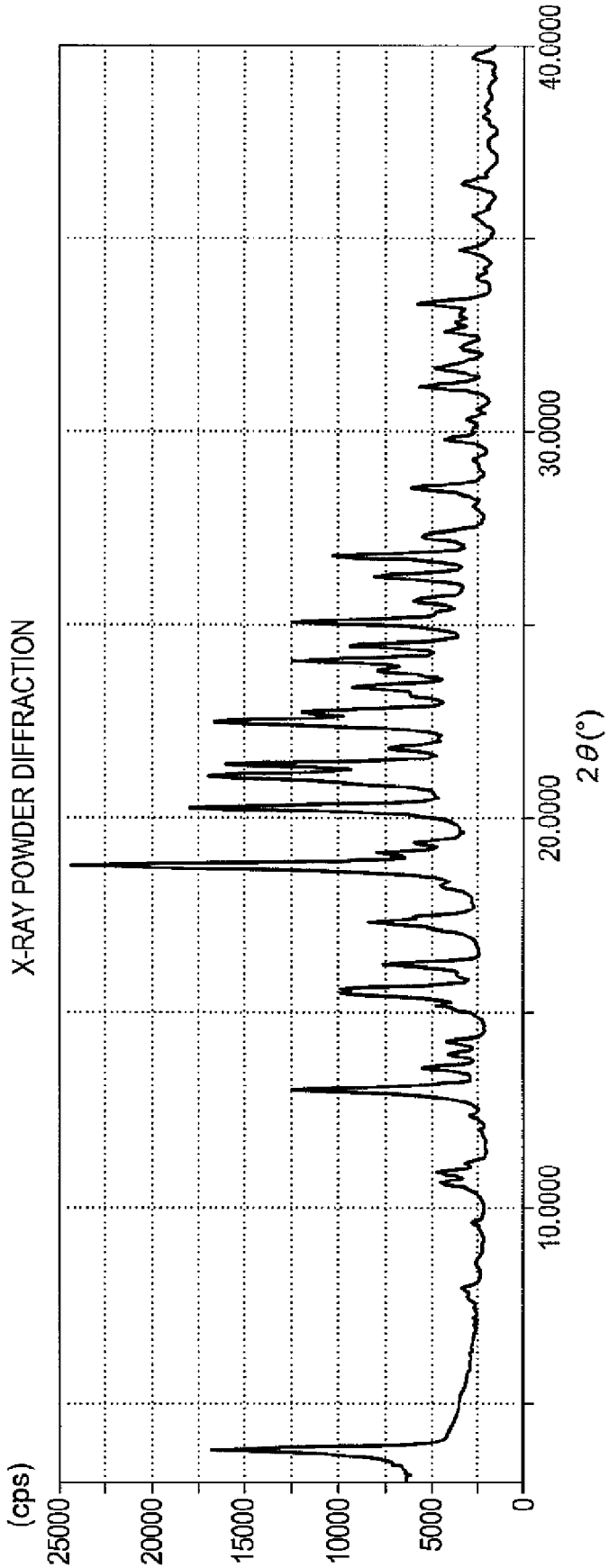

X-RAY POWDER DIFFRACTION
(cps)
25000
20000
15000
10000
5000
0
10.0000
20.0000
30.0000
40.0000
2θ(°)

FIG. 1

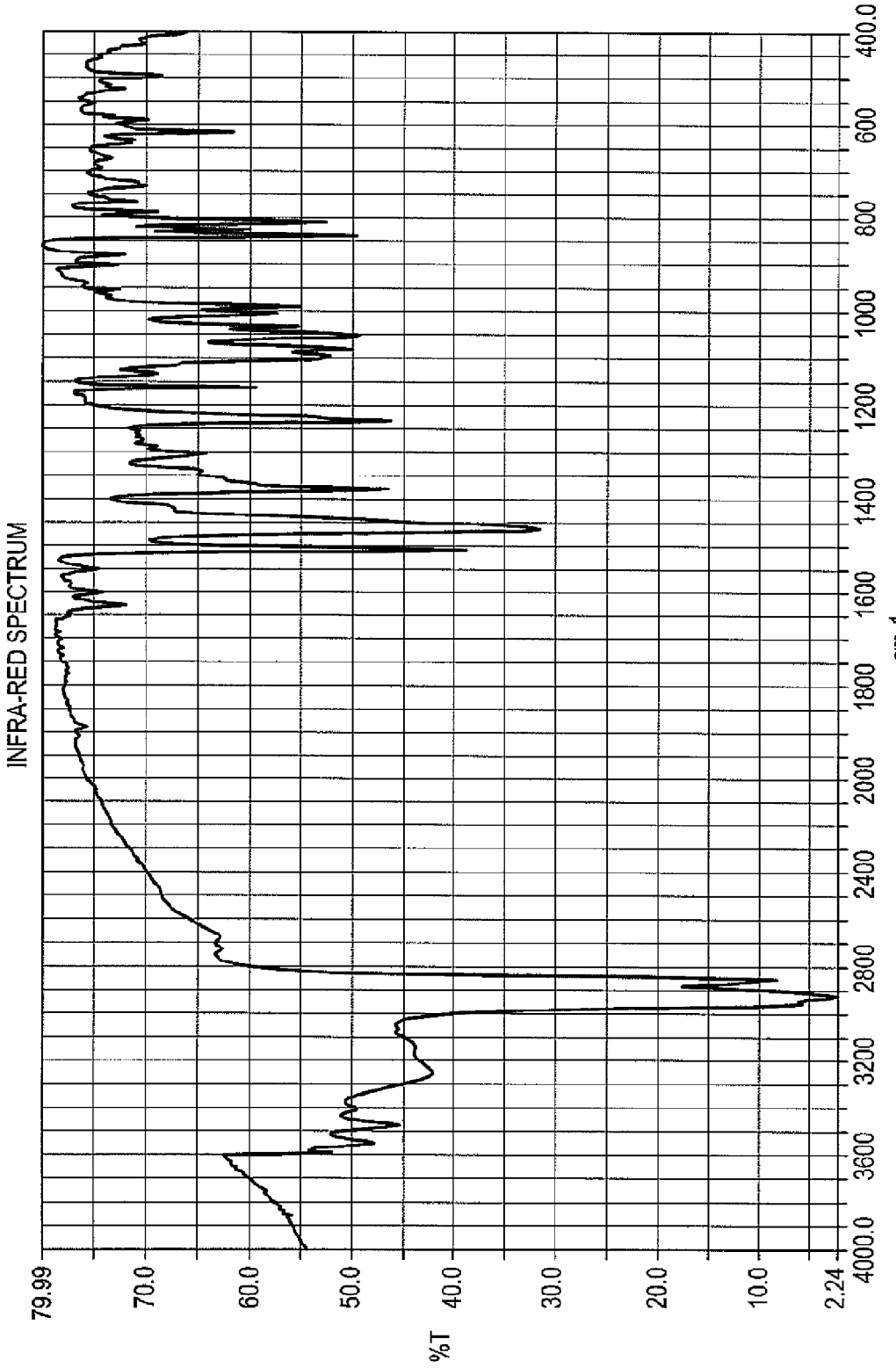

INFRA-RED SPECTRUM
%T
79.99
70.0
60.0
50.0
40.0
30.0
20.0
10.0
2.24
4000.0
3600
3200
2800
2400
2000
1800
1600
1400
1200
1000
800
600
400.0
cm-1

FIG.2

CRYSTALLINE FORM OF 1-(β-D-GLUCOPYRANSOYL)-4-METHYL-3-[5-(4-FLUOROPHENYL)-2-THIENYLMETHYL]BENZENE HEMIHYDRATE

BACKGROUND OF THE INVENTION

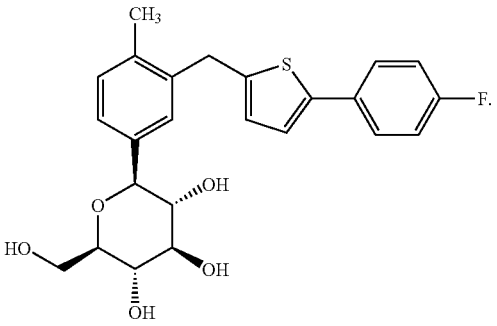
1. Field of the Invention

This invention relates to a crystalline form of 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene hemihydrate useful as an inhibitor of sodium-dependent glucose transporter, to methods for its preparation and isolation, to pharmaceutical compositions which include the compound and a pharmaceutically acceptable carrier, and to pharmaceutical methods of treatment.

2. Description of the Related Art

WO 2005/012326 pamphlet discloses a class of compounds that are inhibitors of sodium-dependent glucose transporter (SGLT) and thus of therapeutic use for treatment of diabetes, obesity, diabetic complications, and the like. There is described in WO 2005/012326 pamphlet 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene of formula (I):

(I)



In general, for commercial use it is important that a product should have good handling qualities. Additionally, there is a need to produce the product in a pure and crystalline form to enable formulations to meet exacting pharmaceutical requirements and specifications.

And it is desirable that the product should be in a form that is readily filterable and easily dried.

Additionally, it is economically desirable that the product be stable for extended periods of time without the need for specialized storage conditions.

But there have been difficulties in obtaining a crystal form of the compound of formula (I) from organic solvents.

It has now been discovered that the compound of formula (I) hemihydrate can be produced in a crystalline form in a manner reproducible on a commercial scale.

SUMMARY OF THE INVENTION

The present invention provides a crystalline form of hemihydrate of the compound of formula (I) as a novel material, in particular in pharmaceutically acceptable form.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1**:

X-ray powder diffraction pattern of the crystalline of hemihydrate of the compound of formula (I).

FIG. **2**:

Infra-red spectrum of the crystalline of hemihydrate of the compound of formula (I).

DETAILED DESCRIPTION OF THE INVENTION

The inventors of the present invention have found that the compounds of formula (I) can be crystallized from a water-containing solvent and the crystalline form of hemihydrate of the compounds (I) have good handling qualities and characteristics.

Accordingly, the present invention is directed to:

1. A crystalline of hemihydrate of 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene.
2. A crystalline of hemihydrate of 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene characterized by a powder x-ray diffraction pattern comprising the following 2θ values measured using CuK_α radiation: 4.36±0.2, 13.54±0.2, 16.00±0.2, 19.32±0.2, 20.80±0.2.
3. A crystalline of hemihydrate of 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene, having substantially the same X-ray powder diffraction pattern as set out in FIG. **1**.
4. A crystalline of hemihydrate of 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene, having substantially the same IR spectrum, as set out in FIG. **2**.
5. A process for the preparation of a crystalline of hemihydrate of 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene, which comprises forming a solution of 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene and crystallizing said hemihydrate from the solution by precipitation or recrystallization.
6. A pharmaceutical composition comprising an effective amount of a crystalline of hemihydrate of 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene and a pharmaceutically acceptable carrier.
7. A method for treatment or delaying the progression or onset of diabetes mellitus, diabetic retinopathy, diabetic neuropathy, diabetic nephropathy, delayed wound healing, insulin resistance, hyperglycemia, hyperinsulinemia, elevated blood levels of fatty acids, elevated blood levels of glycerol, hyperlipidemia, obesity, hypertriglyceridemia, Syndrome X, diabetic complications, atherosclerosis, or hypertension, which comprises administering a therapeutically effective amount of a crystalline of hemihydrate of 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene.

As discussed, the present invention includes a certain solid state crystalline form. Several methods for characterizing such forms exist, and the invention should not be limited by the methods chosen or the instrumentation used in characterizing the compounds of the present invention. For example, with regard to x-ray diffraction patterns, the diffraction peak intensities in the experimental patterns can vary, as is known in the art, primarily due to preferred orientation (non-random orientation of the crystals) in the prepared sample. As such, the scope of the present invention must be considered in light of the variability of characterization that is appreciated by those skilled in the art.

X-Ray Powder Diffraction

The crystalline form of the present invention (I) is characterized by its X-ray powder diffraction pattern. The X-ray diffraction pattern of the crystalline of hemihydrate of the compound (I) was measured on an X-ray diffractometer

(RINT-TTR III, Rigaku, Tokyo, Japan) with measured using CuK_α radiation. Methodology of X-ray powder diffraction is as follows:

Scanning rate: 2.00 degree/minute.

Target: CuK_α.

Voltage: 50 kV.

Current: 300 mA.

Scan range: from 3 to 40.0 degree.

Sampling width: 0.0200 degree.

Infra-Red Spectrum

The infra-red spectrum of the crystalline form of the present invention in mineral oil comprises the following main peaks: 1626, 1600, 1549, and 1507 cm^{-1}.

The infra-red spectrum of crystalline compound (I) hemihydrate is shown in the accompanying drawing in which the ordinate is the transmittance in % and the abscissa is the wavenumber in cm^{-1}.

Thermogravimetric Analysis

The crystalline form of the present invention has been observed to exist in a hemihydrate form. The theoretical water content of the crystalline of the present invention is 1.98%. The thermogravimetric analysis for the crystalline of the present invention shows a mass loss of 1.705%.

Methodology of thermogravimetric analysis is as follows: about 8 mg of compound (I) hemihydrate is weighed and transferred in an aluminum cell holder for TG-50 (Shimadzu, Japan), and then, the thermogravimetric (TG) thermal curve of crystalline compound (I) hemihydrate is determined at a heat rate of 5° C./minute. Typical measuring range is from ambient to 150° C.

The present invention also provides a process for producing the crystalline form of hemihydrate of the compound (I) which comprises forming a solution of compound (I) and precipitating the crystalline form from solution.

Typically, the crystalline of hemihydrate of the compound (I) may be obtained from a mixture of the compound of formula (I), a good solvent and water, optionally containing a poor solvent.

Sometimes some impurities may act as crystallization inhibitors, and impurities need to be removed using a conventional manner, such as silica gel column chromatography. However, the crystalline of hemihydrate of the compound of formula (I) can even be obtained from relatively impure compound (I).

The present invention also provides a pharmaceutical composition comprising the crystalline of hemihydrate of the compound (I) and a pharmaceutically acceptable carrier.

The crystalline compound of the present invention possesses activity as inhibitors of sodium-dependent glucose transporters, and show excellent blood glucose lowering effect.

The crystalline form of the present invention are expected to be useful in the treatment, prevention or delaying the progression or onset of diabetes mellitus (type 1 and type 2 diabetes mellitus, etc.), diabetic complications (such as diabetic retinopathy, diabetic neuropathy, diabetic nephropathy), postprandial hyperglycemia, delayed wound healing, insulin resistance, hyperglycemia, hyperinsulinemia, elevated blood levels of fatty acids, elevated blood levels of glycerol, hyperlipidemia, obesity, hypertriglyceridemia, Syndrome X, atherosclerosis, or hypertension.

The crystalline form of the present invention or a pharmaceutically acceptable salt thereof may be administered either orally or parenterally, and can be used in the form of a suitable pharmaceutical preparation. Suitable pharmaceutical preparations for oral administration include, for example, solid preparations such as tablets, granules, capsules, and powders, or solution preparations, suspension preparations, emulsion preparations, and the like. Suitable pharmaceutical preparations for parenteral administration include, for example, suppositories; injection preparations or intravenous drip preparations, using distilled water for injection, physiological saline solution or aqueous glucose solution; and inhalant preparations.

The pharmaceutical compositions herein will contain, per dosage unit, e.g., tablet, capsule, powder, injection, suppository, teaspoonful and the like, from about 0.01 mg/kg to about 100 mg/kg body weight (preferably from about 0.01 mg/kg to about 50 mg/kg; and, more preferably, from about 0.01 mg/kg to about 30 mg/kg) of the active ingredient, and may be given at a dosage of from about 0.01 mg/kg/day to about 100 mg/kg/day (preferably from about 0.01 mg/kg/day to about 50 mg/kg/day and more preferably from about 0.01 mg/kg/day to about 30 mg/kg/day). The method of treating a disorder described in the present invention may also be carried out using a pharmaceutical composition comprising the crystalline form as defined herein and a pharmaceutical acceptable carrier. The dosage form will contain from about 0.01 mg/kg to about 100 mg/kg (preferably from about 0.01 mg/kg to about 50 mg/kg; and, more preferably, from about 0.01 mg/kg to about 30 mg/kg) of the active ingredient, and may be constituted into any form suitable for the mode of administration selected. The dosages, however, may be varied depending upon administration routes, the requirement of the subjects, the severity of the condition being treated and the compound being employed. The use of either daily administration or post-periodic dosing may be employed.

The crystalline form of the present invention may be used, if necessary, in combination with one or more of other antidiabetic agents, antihyperglycemic agents and/or agents for treatment of other diseases. The present compounds and these other agents may be administered in the same dosage form, or in a separate oral dosage form or by injection.

The dosage of those agents may vary according to, for example, ages, body weight, conditions of patients, administration routes, and dosage forms.

These pharmaceutical compositions may be orally administered to mammalian species including human beings, apes, and dogs, in the dosage form of, for example, tablet, capsule, granule or powder, or parenterally administered in the form of injection preparation, or intranasally, or in the form of transdermal patch.

The crystalline form of hemihydrate of the compound of formula (I) can be prepared from a mixture of the compound (I), a good solvent and water, optionally containing a poor solvent.

Examples of good solvents which have been found suitable include ketones (e.g., acetone, 2-butanone), esters (e.g., ethyl acetate, methyl acetate), alcohols (e.g., methanol, ethanol, i-propanol), and a mixture of these solvents. Examples of poor solvents include alkanes (e.g., hexane, heptane), aromatic hydrocarbons (e.g., benzene, toluene), ethers (e.g., diethyl ether, dimethyl ether, diisopropyl ether) and a mixture of these solvents.

One preferred preparation of the crystalline form of hemihydrate of the compound of formula (I) typically involves dissolving in a good solvent (e.g., ketones or esters) crude or amorphous compound of formula (I) prepared in accordance with the procedures described in WO 2005/012326 pamphlet, and adding water and a poor solvent (e.g., alkanes or ethers) to the resulting solution, followed by filtration.

In case that a good solvent is soluble in water, a poor solvent needs not be used and water may be added to the

solution of the compound of formula (I) in the good solvent so the solubility of the compound of formula (I) can be decreased in the solution.

In case that a poor solvent is used, water is preferably used in amount of 1 to 10 molar equivalents to the compound of formula (I), the good solvent is preferably used in amount of 10 to 100 times of volume of water, and the poor solvent is preferably used in amount of 0.1 to 10 times of volume of the good solvent.

The precise conditions under which the crystalline of hemihydrate of the compound (I) is formed may be empirically determined.

Under these conditions, crystallization can preferably be carried out at a lowered, ambient or elevated temperature.

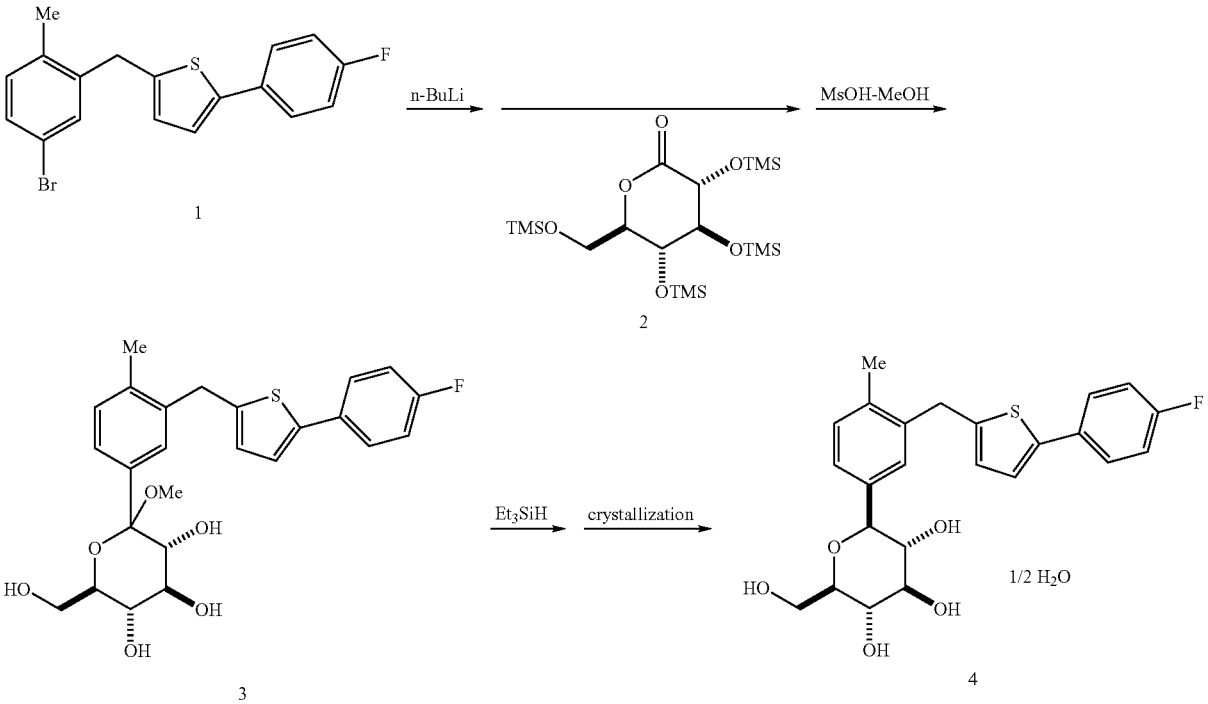
The crystalline form of hemihydrate of the compound of formula (I) is significantly easier to isolate than amorphous form of the compound and can be filtered from the crystallization medium after cooling, and washed and dried. Also, the crystalline form of the present invention is more stable than the amorphous form of the compound of formula (I).

EXAMPLES

Example 1

Crystalline 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene hemihydrate

1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene was prepared in a similar manner as described in WO 2005/012326.



(1) To a solution of 5-bromo-1-[5-(4-fluorophenyl)-2-thienylmethyl]-2-methylbenzene (1, 28.9 g) in tetrahydrofuran (480 ml) and toluene (480 ml) was added n-butyllithium (1.6M hexane solution, 50.0 ml) dropwise at −67 to −70° C. under argon atmosphere, and the mixture was stirred for 20 minutes at the same temperature. Thereto was added a solution of 2 (34.0 g) in toluene (240 ml) dropwise at the same temperature, and the mixture was further stirred for 1 hour at the same temperature. Subsequently, thereto was added a solution of methanesulfonic acid (21.0 g) in methanol (480 ml) dropwise, and the resulting mixture was allowed to warm to room temperature and stirred for 17 hours. The mixture was cooled under ice—water cooling, and thereto was added a saturated aqueous sodium hydrogen carbonate solution. The mixture was extracted with ethyl acetate, and the combined organic layer was washed with brine and dried over magnesium sulfate. The insoluble was filtered off and the solvent was evaporated under reduced pressure. The residue was triturated with toluene (100 ml)—hexane (400 ml) to give 1-(1-methoxyglucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]-benzene (3) (31.6 g). APCI-Mass m/Z 492 ($M+NH_4$).

(2) A solution of 3 (63.1 g) and triethylsilane (46.4 g) in dichloromethane (660 ml) was cooled by dry ice-acetone bath under argon atmosphere, and thereto was added dropwise boron trifluoride•ethyl ether complex (50.0 ml), and the mixture was stirred at the same temperature. The mixture was allowed to warm to 0° C. and stirred for 2 hours. At the same temperature, a saturated aqueous sodium hydrogen carbonate solution (800 ml) was added, and the mixture was stirred for 30 minutes. The organic solvent was evaporated under reduced pressure, and the residue was poured into water and extracted with ethyl acetate twice. The organic layer was washed with water twice, dried over magnesium sulfate and treated with activated carbon. The insoluble was filtered off and the solvent was evaporated under reduced pressure. The residue was dissolved in ethyl acetate (300 ml), and thereto were added diethyl ether (600 ml) and H_2O (6 ml). The mixture was stirred at room temperature overnight, and the

precipitate was collected, washed with ethyl acetate-diethyl ether (1:4) and dried under reduced pressure at room temperature to give 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene hemihydrate (33.5 g) as colorless crystals. mp 98-100° C. APCI-Mass m/Z 462 ($M+NH_4$). ^{1}H-NMR (DMSO-d_6) δ 2.26 (3H, s), 3.13-3.28 (4H, m), 3.44 (1H, m), 3.69 (1H, m), 3.96 (1H, d, J=9.3 Hz), 4.10, 4.15 (each 1H, d, J=16.0 Hz), 4.43 (1H, t, J=5.8 Hz), 4.72 (1H, d, J=5.6 Hz), 4.92 (2H, d, J=4.8 Hz), 6.80 (1H, d, J=3.5 Hz), 7.11-7.15 (2H, m), 7.18-7.25 (3H, m), 7.28 (1H, d, J=3.5 Hz), 7.59 (2H, dd, J=8.8, 5.4 Hz). Anal. Calcd. for $C_{24}H_{25}FO_5S.0.5H_2O$: C, 63.56; H, 5.78; F, 4.19; S, 7.07. Found: C, 63.52; H, 5.72; F, 4.08; S, 7.00.

Example 2

An amorphous powder of 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene (1.62 g) was dissolved in acetone (15 ml), and thereto were added H_2O (30 ml) and a crystalline seed. The mixture was stirred at room temperature for 18 hours, and the precipitate was collected, washed with acetone—H_2O (1:4, 30 ml) and dried under reduced pressure at room temperature to give 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene hemihydrate (1.52 g) as colorless crystals. mp 97-100° C.

The invention claimed is:

1. A crystalline form of 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene hemihydrate.

2. A crystalline form of 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene hemihydrate of claim **1**, having a powder x-ray diffraction pattern comprising the following 2θ values measured using CuK_α radiation: 4.36±0.2, 13.54±0.2, 16.00±0.2, 19.32±0.2, and 20.80±0.2.

3. A crystalline form of 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene hemihydrate of claim **1**, having substantially the same X-ray diffraction pattern as set out in FIG. **1**.

4. A crystalline form of 1-(β-D-glucopyranosyl)-4-methyl-3[5-(4-fluorophenyl)-2-thienylmethyl]benzene hemihydrate of claim **1**, having substantially the same IR spectrum, as set out in FIG. **2**.

5. A process for the preparation of a crystalline form of 1-(β-D-glucopyranosyl) -4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene hemihydrate of claim **1**, which comprises forming a solution of 1-(β-D-glucopyranosyl)-4-methyl-3[5-(4-fluoro-phenyl) -2-thienylmethyl]benzene and crystallizing said hemihydrate from the solution by precipitation or recrystallization.

6. A pharmaceutical composition comprising an effective amount of a crystalline form of 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene hemihydrate of claim **1** and a pharmaceutically acceptable carrier.

7. A method for treatment or delaying the progression or onset of diabetes mellitus, diabetic retinopathy, diabetic neuropathy, diabetic nephropathy, delayed wound healing, insulin resistance, hyperglycemia, hyperinsulinemia, elevated blood levels of fatty acids, elevated blood levels of glycerol, hyperlipidemia, obesity, hypertriglyceridemia, Syndrome X, diabetic complications, atherosclerosis, or hypertension, which comprises administering a therapeutically effective amount of a crystalline form of 1-(β-D-glucopyranosyl)-4-methyl-3[5-(4-fluorophenyl)-2-thienylmethyl]benzene hemihydrate of claim **1** to a subject in need thereof.

* * * * *

EXHIBIT B

US008513202B2

(12) **United States Patent**
Nomura et al.

(10) **Patent No.: US 8,513,202 B2**
(45) **Date of Patent: *Aug. 20, 2013**

(54) **CRYSTALLINE FORM OF 1-(β-D-GLUCOPYRANOSYL)-4-METHYL-3-[5-(4-FLUOROPHENYL)-2-THIENYL-METHYL]BENZENE HEMIHYDRATE**

(75) Inventors: **Sumihiro Nomura**, Osaka (JP); **Eiji Kawanishi**, Osaka (JP)

(73) Assignee: **Mitsubishi Tanabe Pharma Corporation**, Osaka-Shi (JP)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **13/103,557**

(22) Filed: **May 9, 2011**

(65) **Prior Publication Data**

US 2011/0212905 A1 Sep. 1, 2011

Related U.S. Application Data

(63) Continuation of application No. 11/987,670, filed on Dec. 3, 2007, now Pat. No. 7,943,582.

(60) Provisional application No. 60/868,426, filed on Dec. 4, 2006.

(30) **Foreign Application Priority Data**

Dec. 4, 2006 (JP) 2006-327019

(51) **Int. Cl.**
A61K 31/7034 (2006.01)
C07H 7/04 (2006.01)

(52) **U.S. Cl.**
CPC ***A61K 31/7034*** (2013.01); ***C07H 7/04*** (2013.01)
USPC **514/23**; 536/122

(58) **Field of Classification Search**
None
See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

4,160,861	A	7/1979	Cole et al.	
4,584,369	A	4/1986	Klein et al.	
5,149,838	A	9/1992	Humphrey et al.	
5,424,406	A	6/1995	Tsujihara et al.	
5,731,292	A	3/1998	Tsujihara et al.	
5,767,094	A	6/1998	Tsujihara et al.	
5,780,483	A	7/1998	Widdowson et al.	
5,830,873	A	11/1998	Tsujihara et al.	
6,048,842	A	4/2000	Tsujihara et al.	
6,153,632	A	11/2000	Rieveley	
6,297,363	B1	10/2001	Kubo et al.	
6,414,126	B1	7/2002	Ellsworth et al.	
6,515,117	B2	2/2003	Ellsworth et al.	
6,562,791	B1	5/2003	Maurya et al.	
6,617,313	B1	9/2003	Maurya et al.	
6,627,611	B2	9/2003	Tomiyama et al.	
7,375,213	B2	5/2008	Deshpande et al.	
7,511,022	B2	3/2009	Beavers et al.	
7,943,582	B2 *	5/2011	Nomura et al.	514/23
2001/0041674	A1	11/2001	Tomiyama et al.	
2002/0032164	A1	3/2002	Dale et al.	
2002/0052326	A1	5/2002	Washburn	
2002/0111315	A1	8/2002	Washburn et al.	
2003/0024914	A1	2/2003	Aleshin	
2003/0064935	A1	4/2003	Gougoutas	
2003/0087843	A1	5/2003	Washburn	
2003/0114390	A1	6/2003	Washburn et al.	
2004/0053855	A1	3/2004	Fujikura et al.	
2004/0063646	A1	4/2004	Fujikura et al.	
2004/0110936	A1	6/2004	Ohsumi et al.	
2004/0116357	A1	6/2004	Fushimi et al.	
2004/0132669	A1	7/2004	Nishimura et al.	
2004/0138143	A1	7/2004	Glombik et al.	
2004/0259819	A1	12/2004	Frick et al.	
2005/0014704	A1	1/2005	Frick et al.	
2005/0032711	A1	2/2005	Patel et al.	
2005/0032712	A1	2/2005	Urbanski	
2005/0037980	A1	2/2005	Rybczynski et al.	
2005/0037981	A1	2/2005	Beavers et al.	
2005/0124556	A1	6/2005	Burton	
2005/0233988	A1	10/2005	Nomura et al.	
2006/0217323	A1	9/2006	Patel et al.	
2006/0229260	A1	10/2006	Rybczynski et al.	
2006/0234954	A1	10/2006	Urbanski	
2006/0293251	A1	12/2006	Urbanski et al.	
2007/0060545	A1	3/2007	Nomura et al.	

FOREIGN PATENT DOCUMENTS

CA	2494177	A1	2/2004
EP	0355750	A1	2/1990
EP	0579204	A2	1/1994
EP	0579204	A3	1/1994
EP	1338603	A1	8/2003
EP	1528066	A1	5/2005

(Continued)

OTHER PUBLICATIONS

Ahmad et al., "Synthesis and Structure Determination of Some Oxadiazole-2-Thione and Triazole-3-Thione Galactosides", Nucleosides, Nucleotides & Nucleic Acids, vol. 20, No. 9, 2001, pp. 1671-1682.

Amishiro, N. et al., "Synthesis and Antitumor Activity of Duocarmycin Derivatives: A-Ring Pyrrole Compounds Bearing 5-Membered Heteroarylacryloyl Groups," Chem. Pharm. Bull., Oct. 1999, vol. 47, No. 10, pp. 1393-1403.

Appleton et al, "A Mild and Selective C-3 Reductive Alkylation of Indoles", Tetrahedron Letters, vol. 34, No. 9, 1993, pp. 1529-1532.

Arakawa et al, "Improved diabetic syndrome in C57BL/KsJ-db/db mice by oral administration of the Na+ -glucose cotransporter inhibitor T-1095," British Journal of Pharmacology, vol. 132, 2001, pp. 578-586.

(Continued)

Primary Examiner — Eric S Olson
(74) *Attorney, Agent, or Firm* — Birch, Stewart, Kolasch & Birch, LLP

(57) **ABSTRACT**

A novel crystal form of 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene hemihydrate, and having favorable characteristics, is characterized by its x-ray powder diffraction pattern and/or by its infra-red spectrum.

5 Claims, 2 Drawing Sheets

(56) **References Cited**

FOREIGN PATENT DOCUMENTS

GB	2359554	A	8/2001
JP	63-233975	A	9/1988
JP	4-253974	A	9/1992
JP	9-263549	A	10/1997
JP	10-324632	A	12/1998
JP	2000-34230	A	2/2000
JP	2000-34239	A	2/2000
JP	2001-288178	A	10/2001
JP	2003-12686	A	1/2003
WO	WO 93/21178	A1	10/1993
WO	WO 97/25033	A1	7/1997
WO	WO 00/74681	A1	12/2000
WO	WO 01/27128	A1	4/2001
WO	WO 01/64669	A1	9/2001
WO	WO 01/68660	A1	9/2001
WO	WO 01/74834	A1	10/2001
WO	WO 01/74835	A1	10/2001
WO	WO 02/053573	A1	7/2002
WO	WO 02/068439	A1	9/2002
WO	WO 02/068440	A1	9/2002
WO	WO 02/070020	A2	9/2002
WO	WO 02/083066	A2	10/2002
WO	WO 02/088157	A1	11/2002
WO	WO 02/094262	A1	11/2002
WO	WO 03/000712	A1	1/2003
WO	WO 03/011880	A1	2/2003
WO	WO 03/020737	A1	3/2003
WO	WO 03/043621	A1	5/2003
WO	WO 03/087104	A1	10/2003
WO	WO 03/099836	A1	12/2003
WO	WO 2004/007517	A1	1/2004
WO	WO 2004/013118	A1	2/2004
WO	WO 2004/014931	A1	2/2004
WO	WO 2004/018442	A1	3/2004
WO	WO 2004/019958	A1	3/2004
WO	WO 2004/052902	A1	6/2004
WO	WO 2004/052903	A1	6/2004
WO	WO 2004/063209	A2	7/2004
WO	WO 2004/080990	A1	9/2004
WO	WO 2004/087727	A1	10/2004
WO	WO 2004/099230	A1	11/2004
WO	WO 2004/113359	A1	12/2004
WO	WO 2005/012326	A1	2/2005
WO	WO 2005/030127	A2	4/2005
WO	WO 2006/108842	A1	10/2006
WO	WO 2006/120208	A1	11/2006
WO	WO 2007/035198	A1	3/2007
WO	WO 2007/054978	A2	5/2007
WO	WO 2007/107354	A1	9/2007

OTHER PUBLICATIONS

Banker et al. (Editors), Modern Pharmaceutics, Third Edition, published 1996, p. 596, Marcel Dekker, Inc.

Benhaddou et al.,"Tetra-n-propylammonium tetraoxoruthenate(VII): a reagent of choice for the oxidation of diversely protected glycopyranoses and glycofuranoses to lactones", Carbohydrate Research, vol. 260, 1994, pp. 243-250.

Bertolini et al., "A New Simple One-Pot Regioselective Preparation of Mixed Diesters of Carbonic Acid.", Journal of Organic Chemistry, vol. 63, No. 17, 1998, pp. 6031-6034.

Blair et al., "Effect of Ring Fluorination on the Pharmacology of Hallucinogenic Tryptamines", J. Med. Chem., vol. 43, 2000, pp. 4701-4710.

Boehm et al., "Novel Inhibitors of DNA Gyrase: 3D Structure Based Biased Needle Screening, Hit Validation by Biophysical Methods, and 3D Guided Optimization. A Promising Alternative to Random Screening," J. Med. Chem., vol. 43, No. 14, 2000, pp. 2664-2674.

Bookser, B.C., "2-Benzyloxymethyl-5-(tributylstannyl)tetrazole. A reagent for the preparation of 5-aryl-and 5-heteroaryl-1H-tetrazoles via the Stille reaction," Tetrahedron Letters, 2000, vol. 41, pp. 2805-2809.

Bouillon, A. et al, "Synthesis of novel halopyridinylboronic acids and esters. Part 2: 2,4, or 5-Halopyridin-3-yl-boronic acids and esters," Tetrahedron, 2002, vol. 58, pp. 3323-3328.

Bouillon, A. et al, "Synthesis of novel halopyridinylboronic acids and esters. Part 3: 2, or 3-Halopyridin-4-yl-boronic acids and esters," Tetrahedron, 2002, vol. 58, pp. 4369-4373.

Bouillon, A. et al, "Synthesis of novel halopyridinylboronic acids and esters. Part 4: Halopyridin-2-yl-boronic acids and esters are stable, crystalline partners for classical Suzuki cross-coupling," Tetrahedron, 2003, vol. 59, pp. 10043-10049.

Brooks et al., "Boron Trichloride/Tetra-n-Butylammonium Iodide: A Mild, Selective Combination Reagent for the Cleavage of Primary Alkyl Aryl Ethers", J. Org. Chem., vol. 64, 1999, pp. 9719-9721.

CAS Reg. No. 487001-40-1, IPOrganisers, Entered STN Feb. 7, 2003, pp. 1-2.

Cicchillo, R.M. et al, "A convenient synthesis of glycosyl chlorides from sugar hemiacetals using triphosgene as the chlorine source," Carbohydrate Research, 2000, vol. 328, pp. 431-434.

Clayden, J. et al, "Dearomatizing Cyclization of Arylsulfonylalkoxymethyl Lithiums: A Route to the Podophyllotoxin Skeleton," Organic Letters, 2003, vol. 5, No. 6, pp. 831-834.

Comins et al., "Synthesis of 3-Substituted Indoles Via N-Acylindolium Ions", Tetrahedron Letters, vol. 27, No. 17, 1986, pp. 1869-1872.

Cottet, F. et al, "Recommendable Routes to Trifluoromethyl-Substituted Pyridine- and Quinolinecarboxylic Acids," Eur. J. Org. Chem., 2003, pp. 1559-1568.

Czernecki et al., "C-Glycosides. 7. Stereospecific C-Glycosylation of Aromatic and Heterocyclic Rings", J. Org. Chem., vol. 54, 1989, pp. 610-612.

De Las Heras, F. G. et al, "Alkylating Nucleosides 1. Synthesis and Cytostatic Activity of N-Glycosyl(halomethyl)-1,2,3-triazoles. A New Type of Alkylating Agent," Journal of Medicinal Chemistry, 1979, vol. 22, No. 5, pp. 496-501.

Deeg et al., "Pioglitazone and Rosiglitazone Have Different Effects on Serum Lipoprotein Particle Concentrations and Sizes in Patients With Type 2 Diabetes and Dyslipidemia.", Diabetes Care, vol. 30, No. 10, Oct. 2007, pp. 2458-2464.

Deetjen et al., "Renal Handling of D-Glucose and Other Sugars", Textbook of Nephrology, vol. 1, 3rd Edition, 1995, pp. 90-94.

Devivar et al., "Benzimidazole Ribonucleosides: Design, Synthesis, and Antiviral Activity of Certain 2-(Alkylthio)- and 2-(Benzylthio)-5,6-dichloro-1-(β-D-ribofuranosyl)benzimidazoles1," J.Med. Chem., vol. 37, 1994, pp. 2942-2949.

Dewynter et al., "Synthesis of Pseudonucleosides containing Chiral Sulfahydantoins as Aglycone (II)", Tetrahedron, vol. 52, No. 3, 1996, pp. 993-1004.

Dillard et al., "Indole Inhibitors of Human Nonpancreatic Secretory Phospholipase A2. 1. Indole-3-acetamides", J. Med. Chem., vol. 39, 1996, pp. 5119-5136.

Dondoni et al., "Stereoselective synthesis of C-glycosylphosphonates from their ketols. Reconsideration of an abandoned route", Tetrahedron: Asymmetry, vol. 11, 2000, pp. 305-317.

Dondoni et al., "Thiazole-Based Synthesis of Formyl C-Glycosides", J. Org. Chem., vol. 59, 1994, pp. 6404-6412.

Dudash, Jr. et al, "Glycosylated dihydrochalcones as potent and selective sodium glucose co-transporter 2 (SGLT2) inhibitors," Bioorganic & Medicinal Chemistry Letters, vol. 14, 2004, pp. 5121-5125.

Dunn et al., "Analgetic and antiinflammatory 7-Aroylbenzofuran-5-ylacetic acids and 7-Aroylbenzothiophene-5-ylacetic Acids.", Journal of Med. Chem., vol. 29, No. 1, 1986, pp. 2326-2329.

Eid et al., "Reaction of Some 1,2,4-Triazines with Acetobromoglucose", Arch. Pharm. (Weinheim), vol. 323, 1990, pp. 243-245.

Ellsworth et al, "Aglycone exploration of C-arylglucoside inhibitors of renal sodium-dependent glucose transporter SGLT2," Bioorganic & Medicinal Chemistry Letters, vol. 18, 2008, pp. 4770-4773.

Ellsworth et al., "C-Arylglucoside synthesis: triisopropylsilane as a selective reagent for the reduction of an anomeric C-phenyl ketal," Tetrahedron: Asymmetry, vol. 14, 2003, pp. 3243-3247.

Frahn, J. et al, "Functionalized AB-Type Monomers for Suzuki Polycondensation," Synthesis, Nov. 1997, pp. 1301-1304.

Fresneda et al., "Synthesis of the indole alkaloids meridianins from the tunicate Aplidium meridianum," Tetrahedron, vol. 57, 2001, pp. 2355-2363.
Fuller, L.S. et al, "Thienothiophenes. Part 2. Synthesis, metallation and bromine-lithium exchange reactions of thieno[3,2-b-thiophene and its polybromo derivatives," J. Chem. Soc., Perkin Trans. 1., 1997, pp. 3465-3470.
Ganesh, T. et al, "Synthesis and biological evaluation of fluorescently labeled epothilone analogs for tubulin binding studies," Tetrahedron, 2003, vol. 59, pp. 9979-9984.
Gershell, "Type 2 diabetes market", Nature Reviews Drug Discovery, vol. 4, May 2005, pp. 367-368.
Gohier, F. et al, "ortho-Metalation of Unprotected 3-Bromo and 3-Chlorobenzoic Acids with Hindered Lithium Dialkylamides," J. Org. Chem., 2003, vol. 68, pp. 2030-2033.
Goodman & Gilman's The Pharmacological Basis of Therapeutics, 10th Edition, McGraw-Hill Medical Publishing Division, 2001, pp. 54-57.
Gronowitz, S. et al, "Some Substitution Reactions of 1-(2-Thienyl)pyrazole and 1-(3'-Thienyl)pyrazole," Chemica Scripta., 1979, vol. 13, pp. 157-161.
Gros, P. et al, "Efficient and Regioselective Access to Bis-heterocycles via Palladium-Catalysed Coupling of Organostannanes and Organozincates Derived from C-6 Lithiated 2-Methoxypyridine," Synthesis, 1999, No. 5, pp. 754-756.
Han et al., "Dapagliflozin, A Selective SGLT2 Inhibitor, Improves Glucose Homeostasis in Normal and Diabetic Rats", Diabetes, vol. 57, Jun. 2008, pp. 1723-1729.
Handlon, "Sodium glucose co-transporter 2 (SGLT2) inhibitors as potential antidiabetic agents," Expert Opin. Ther. Patents, vol. 15, No. 11, 2005, pp. 1531-1540.
Hofslokken et al., "Convenient Method for the ortho-Formylation of Phenols.", Acta Chemica Scandinavica, vol. 53, 1999, pp. 258-262.
Hongu et al., "Na+-Glucose Cotransporter Inhibitors as Antidiabetic Agents. II.1) Synthesis and Structure—Activity Relationships of 4'-Dehydroxyphlorizin Derivatives", Chem. Pharm. Bull., vol. 46, No. 1, 1998, pp. 22-33.
Horton et al., "Synthetic Routes to Higher-Carbon Sugars. Reaction of Lactones with 2-Lithio-1,3-Dithiane", Carbohydrate Research, vol. 94, 1981, pp. 27-41.
Hu et al., "A New Approach Towards the Yellowing Inhibition of Mechanical Pulps. Part I: Selective Removal of alpha-Hydroxyl and alpha-Carbonyl Groups in Lignin Model Compounds", Holzforschung, vol. 53, No. 1, 1999, pp. 43-48.
Huang-Minlon, "Reduction of Steroid Ketones and other Carbonyl Compounds by Modified Wolff-Kishner Method", J. Am. Chem. Soc., vol. 71, Oct. 1949, pp. 3301-3303.
Ibrahim et al., "Selective Synthesis and Structure of 2-N- and 3-S-Glucosyl-1,2,4-Triazoles of Potential Biological Interest", Carbohydrate Letters, vol. 3, No. 5, 1999, pp. 331-338.
Ibrahim, "Facile Approach for the Selective Glycosidation of Cyclic Asymmetric Amides and Thioamides", Carbohydrate Letters, vol. 1, 1996, pp. 425-432.
Information Submission of Sep. 1, 2009 in U.S. Appl. No. 11/045,446, including Appendices A, B and C.
International Search Report for Application No. PCT/JP2004/011312, dated Nov. 25, 2004.
Isaji, "Sodium-glucose cotransporter inhibitor for diabetes," Current Opinion in Investigational Drugs, vol. 8, No. 4, 2007, pp. 285-292.
Kahn et al, "Normalization of Blood Glucose in Diabetic Rats with Phlorizin Treatment Reverses Insulin-resistant Glucose Transport in Adipose Cells without Restoring Glucose Transporter Gene Expression," J. Clin. Invest., vol. 87, Feb. 1991, pp. 561-570.
Kanai et al., "The Human Kidney Low Affinity Na+/Glucose Cotransporter SGLT2: Delineation of the Major Renal Reabsorptive Mechanism for D-Glucose", J. Clin. Invest., vol. 93, Jan. 1994, pp. 397-404.
Kasahara et al., "A missense mutation in the Na+/glucose cotransporter gene SGLT1 in a patient with congenital glucose-galactose malabsorption: normal trafficking but inactivation of the mutant protein," Biochimica et Biophysica Acta, vol. 1536, 2001, pp. 141-147.
Katz et al., "Quantitative Insulin Sensitivity Check Index: A Simple, Accurate Method for Assessing Insulin Sensitivity in Humans.", J. of Clin. Endrocrinology & Metabolism, vol. 85, No. 7, 2000, pp. 2402-2410.
Ketcha et al., "Synthesis of Alyl-Substituted N-Protected Indoles via Acylation and Reductive Deoxygenation1" J. Org. Chem., vol. 54, 1989, pp. 4350-4356.
Khan et al, "Reactions of Phenyl-Substituted Heterocyclic Compounds—II. Nitrations and Brominations of 1-Phenylpyrazole Derivatives," Canadian Journal of Chemistry, vol. 41, 1963, pp. 1540-1547.
Lee, J. S. et al, "Synthesis and in Vitro Activity of Novel Isoxazolyl Tetrahydropyridinyl Oxazolidinone Antibacterial Agents," Bioorganic & Medicinal Chemistry Letters, 2003, vol. 13, pp. 4117-4120.
Liang et al., "JNJ-28431754/TA-7284, an Inhibitor of Sodium-Glucose Cotransporter 2, Ameliorates Diabetic Syndrome in the Zucker Diabetic Fatty Rat," Oct. 2009, Poster presented at International Diabetes Federation 20th World Diabetes Congress, Montreal, Canada.
Liang et al., "JNJ-28431754/TA-7284, an Inhibitor of Sodium-Glucose Cotransporter 2, Reduces Body Weight Gain in Zucker Fatty Rats," Oct. 2009, Poster presented at International Diabetes Federation 20th World Diabetes Congress, Montreal, Canada.
Liang et al., "JNJ-28431754/TA-7284, an SGLT Inhibitor, Lowers Blood Glucose and Reduces Body Weight in Obese and type 2 Diabetic Animal Models," Jun. 2009.
Lin et al., "Syntheses of Guanidinoglycosides with the Inventive use of Mitsunobu Conditions and 1, 8-Diazabicyclo[5.4.0]undec-7-ene.", Synthesis, No. 2, 2003, pp. 255-261.
Link et al., "A method for preparing C-glycosides related to phlorizin" Tetrahedron Letters, vol. 41, 2000, pp. 9213-9217.
Lipscombe et al., "Trends in diabetes prevalence, incidence, and mortality in Ontario, Canada 1995-2005: a population-based study", Lancet, vol. 369, 2007, pp. 750-756.
Maatooq, "C-p-Hydroxybenzoylglycoflavones from Citrullus Colocynthis", Phytochemistry, vol. 44, No. 1, Jan. 1997, pp. 187-190.
Mackenzie et al., "Biophysical Characteristics of the Pig Kidney Na+/Glucose Cotransporter SGLT2 Reveal a Common Mechanism for SGLT1 and SGLT2", J. Biol. Chem., vol. 271, No. 5, 1996, pp. 32678-32683.
Manis et al., "Metabolism of 4,4'-Methylenebis(2-chloroaniline) By Canine Liver and Kidney Slices.", Drug Metabolism and Disposition, vol. 14, No. 2, 1986, pp. 166-174.
Marsenic, "Glucose Control by the Kidney: An Emerging Target in Diabetes.", Am. J. of Kidney Diseases, vol. 53, No. 5, May 2009, pp. 875-883.
Matsuda et al., "Insulin Sensitivity Indices Obtained From Oral Glucose Tolerance Testing: Comparison with the euglycemic insulin clamp," Diabetes Care, vol. 22, No. 9, Sep. 1999, pp. 1462-1470.
Matthews et al., "Homeostasis model assessment: insulin resistance and β-cell function from fasting plasma glucose and insulin concentrations in man," Diabetolgia, vol. 28, 1985, pp. 412-419.
Meanwell et al., "Regiospecific Functionalization of 1,3-Dihydro-2H-benzimidazol-2-one and Structurally Related Cyclic Urea Derivates.", J. Org. Chemistry, vol. 60, No. 6, 1995, pp. 1565-1582.
Meng et al., "Discovery of Dapagliflozin: A Potent, Selective Renal Sodium-Dependent Glucose Cotransporter 2 (SGLT2) Inhibitor for the Treatment of Type 2 Diabetes", J. Med. Chem., vol. 51, No. 5, 2008, pp. 1145-1149.
Messaoudi, S. et al, "Synthesis and biological evaluation of oxindoles and benzimidazolinones derivatives," European Journal of Medicinal Chemistry, 2004, vol. 39, pp. 453-458.
Mewshaw et al., "New Generation Dopaminergic Agents. 7. Heterocyclic Bioisosteres that Exploit the 3-OH-Phenoxyethylamine D2 Template", Bioorganic & Medicinal Chemistry Letters, vol. 9, 1999, pp. 2593-2598.
Miyaura et al., "Palladium-Catalyzed Cross-Coupling Reactions of Organoboron Compounds.", Chem. Rev., vol. 95, No. 7, 1995, pp. 2457-2483.

Nishimura et al, "Tissue-specific mRNA Expression Profiles of Human ATP-binding Cassette and Solute Carrier Transporter Superfamilies," Drug Metab. Pharmacokinet., vol. 20, No. 6, 2005, pp. 452-477.
Nomura et al., "Discovery of Novel C-glucosides with Thiophene Ring as Sodium-dependent Glucose Cotransporter 2 Inhibitors for the Treatment of Type 2 Diabetes Mellitus", MEDI 151, Abstract, The 238th ACS National Meeting, Washington, DC, Aug. 16-20, 2009; American Chemical Society: Washington, D.C.
Nomura, "Renal Sodium-Dependent Glucose Cotransporter 2 (SGLT2) Inhibitors for New Anti-Diabetic Agent," Current Topics in Medicinal Chemistry, vol. 10, No. 4, 2010, pp. 411-418.
Notice of pre-grant Opposition from counterpart Costa Rica Appl. No. 10861, pp. 1-9.
Office Action in U.S. Appl. No. 11/045,446, dated Dec. 5, 2008.
Office Action in U.S. Appl. No. 11/045,446, dated Jun. 16, 2008.
Office Action in U.S. Appl. No. 11/045,446, dated Oct. 1, 2009.
Ohsumi et al. "Pyrazole-O-Glucosides as Novel Na+ -Glucose Cotransporter (SGLT) Inhibitors" Bioorganic & Medicinal Chemistry Letters, vol. 13, 2003, pp. 2269-2272.
Oku et al., "T-1095, an Inhibitor of Renal Na+-Glucose Cotransporters, May Provide a Novel Approach to Treating Diabetes", Diabetes, vol. 48, Sep. 1999, pp. 1794-1800.
Opposition to an Invention Patent (and English translation thereof) from counterpart Costa Rica application 11.263.
Opposition to an Invention Patent from counterpart Costa Rica Appl. No. 10861, pp. 1-9.
Orjales et al. "New 2-Piperazinylbenzimidazole Derivatives as 5-HT-3 Antagonists. Synthesis and Pharmacological Evaluation," J. Med. Chem., vol. 40, 1997, pp. 586-593.
Parker, K. A. et al, "Reductive Aromatization of Quinols: Synthesis of the C-Arylglycoside Nucleus of the Paulacandins and Chaetiacandin," Organic Letters, 2000, vol. 2, No. 4, pp. 497-499.
Patani et al., "Bioisosterism: A Rational Approach to Drug Design", Chem. Rev., American Chemical Society, vol. 96, 1996, pp. 3147-3176.
Peng et al., "Post-transcriptional Regulaton of Na+/Glucose Cotransporter (SGTL1) Gene Expression in LLC-PK1 Cells.", Journal of Biological Chemistry, vol. 270, No. 35, 1995, pp. 20536-20542.
Polidori et al., "Frequently Used Insulin Sensitivity Measures May Be Inappropriate for Subjects Treated With SGLT2 Inhibitors," Jun. 2009, Poster presented at the American Diabetes Assoc. 69th Scientific Sessions, Jun. 5-9, 2009, New Orleans, LA.
Raynaud et al., "Revised Concept for the Estimation of Insulin Sensitivity From a Single Sample.", Diabetes Care, vol. 22, No. 6, Jun. 1999, pp. 1003-1004.
Rossetti et al, "Correction of Hyperglycemia with Phlorizin Normalizes Tissue Sensitivity to Insulin in Diabetic Rats," J. Clin. Invest., vol. 79, May 1987, pp. 1510-1515.
Rossetti et al, "Effect of Chronic Hyperglycemia on in Vivo Insulin Secretion in Partially Pancreatectomized Rats," J. Clin. Invest., vol. 80, Oct. 1987, pp. 1037-1044.
Rossetti et al., "Glucose Toxicity," Diabetes Care, vol. 13, Issue 6, 1990, pp. 610-630, Abstract only.
Schmidt, R. R. et al, "Synthese von Pyrazol-, Pyrazolo[3,4-d]pyrimidin-und 1H-1,2,4-Triazolgluconucleosiden aus Glucosehydrazonen," Liebigs Ann. Chem., 1981, pp. 2309-2317.
Silverman, "The Organic Chemistry of Drug Design and Drug Action," Academic Press, 1992, pp. 19-23.
Somei et al., "The First and Simple Total Synthesis of Capparilosides A1," Heterocycles, vol. 53, No. 7, 2000, pp. 1573-1578.
Srogl et al., "Sulfonium Salts. Participants par Excellence in Metal-Catalyzed Carbon-Carbon Bond-Forming Reactions", J. Am. Chem. Soc., vol. 119, No. 50, 1997, pp. 12376-12377.
Stoner et al, "Benzylation via Tandem Grignard Reaction - Iodotrimethylsilane (TMSI) Mediated Reduction," Tetrahedron, vol. 51, No. 41, 1995, pp. 11043-11062.
Stumvoll et al., "Use of the Oral Glucose Tolerance Test to Assess Insulin Release and Insulin Sensitivity.", Diabetes Care, vol. 23, No. 3, Mar. 2000, pp. 295-301.
Tanaka et al. "Solid-Phase Synthesis of β-Mono-Substituted Ketones and an Application to the Synthesis of a Library of Phlorizin Derivatives", Synlett, No. 9, 2002, pp. 1427-1430.
The State Intellectual Property Office of P.R. China Office Action, Appl. No. 2004800220078, Dec. 26, 2008, pp. 1-6, Second Office Action, English translation.
The State Intellectual Property Office of P.R. China Office Action, Appl. No. 2004800220078, Oct. 19, 2007, pp. 1-6, First Office Action, English translation.
The State Intellectual Property Office of P.R. China the Decision of Rejection (PCT) Action, Appl. No. 2004800220078, Nov. 2009, pp. 1-7.
The State Intellectual Property Office of P.R. China, Observations (1st), Appl. No. 2004800220078, May 2008, pp. 1-3, English translation.
The State Intellectual Property Office of P.R. China, Observations (2nd), Appl. No. 2004800220078, May 2009, pp. 1-4, English translation.
The State Intellectual Property Office of P.R. China, Record of Interview, Appl. No. 2004800220078, Sep. 2009, pp. 1-7, English translation.
The State Intellectual Property Office of P.R. China, Response to the Decision of Rejection (PCT), Appl. No. 2004800220078, Feb. 2010, pp. 1-27, English translation.
Thornber, "Isosterism and Molecular Modification in Drug Design", Chemical Society Reviews, vol. 8, 1979, pp. 563-580.
Tilak, B.D. et al, "Carcinogenesis by Thiophene Isosters of Polycyclic Hydrocarbons," Tetrahedron, 1960, vol. 9, pp. 76-95.
Tsujihara et al, "Na+-Glucose Cotransporter (SGLT) Inhibitors as Antidiabetic Agents. 4. Synthesis and Pharmacological Properties of 4'-Dehydroxyphlorizip Derivatives Substituted on the B Ring," J. Med. Chem., vol. 42, No. 26, 1999, pp. 5311-5324.
Tsujihara et al., "Na+ -Glucose Cotransporter Inhibitors as Antidiabetic.l. Synthesis and Pharmacological Properties of 4'-Dehydroxyphlorizin Derivatives Based on a New Concept," Chem. Pharm. Bull., vol. 44, No. 6, 1996, pp. 1174-1180.
Tsujihara et al., Bio Clinica, vol. 13, No. 4, 1998, pp. 324-328, English language Abstract.
Turk et al., "Glucose/galactose malabsorption caused by a defect in the Na+/glucose cotransporter," Nature, vol. 350, Mar. 1991, pp. 354-356.
Ueta et al, "Anti-diabetic and Anti-obesity effects of TA-7284, a Novel SGLT2 Inhibitor," Partial English translation, JDS Poster Presentation, 2009.
Ueta et al, "Long-term treatment with the Na+-glucose cotransporter inhibitor T-1095 causes sustained improvement in hyperglycemia and prevents diabetic neuropathy in Goto-Kakizaki Rats," Life Sciences, vol. 76, 2005, pp. 2655-2668.
Unger et al., "Hyperglycaemia as an inducer as well as a consequence of impaired islet cell function and insulin resistance: implications for the management of diabetes.", Diabetologia, vol. 28, 1985, pp. 119-121.
Wallace et al., "Use and Abuse of HOMA Modeling.", Diabetes Care, vol. 27, No. 6, Jun. 2004, pp. 1487-1495.
Wang et al, "Selective monolithiation of 2,5-dibromopyridine with butyllithium," Tetrahedron Letters, vol. 41, 2000, pp. 4335-4338.
Wareham et al., "Is There Really an epidemic of diabetes?", Diabetologia, vol. 48, 2005, pp. 1454-1455.
Washburn, "Evolution of sodium glucose co-transporter 2 inhibitors as anti-diabetic agents," Expert Opin. Ther. Patents, vol. 19, No. 11, 2009, pp. 1485-1499.
Wild et al., "Global Prevalence of Diabetes: Estimates for the year 2000 and projections for 2030," Diabetes Care, vol. 27, No. 5, May 2004, pp. 1047-1053.
Wolff, vol. 1: Principles and Practice, Burger's Medicinal Chemistry and Drug Discovery, 5th Edition, 1995, pp. 975-977.
Wright, "Renal Na+-glucose cotransporters," Am J Physiol Renal Physiol, vol. 280, 2001, pp. F10-F18.
Yang et al., "Convergent C-Glycolipid Synthesis via the Ramberg-Backlund Reaction: Active Antiproliferative Glycolipids", vol. 1, No. 13, Org. Lett. 1999, pp. 2149-2151.
Yoshimura, H. et al, "Discovery of Novel and Potent Retinoic Acid Receptor alpha- Agonists: Synthesis and Evaluation of

Benzofuranyl-pyrrole and Benzothiophenyl-pyrrole Derivatives," J. Med. Chem., 2000, vol. 43, pp. 2929-2937.
Zamani, "Synthesis and Structure Determination of Some New N-Glycosides of 4,5-Disubstituted-1,2,4-triazole-3-thiones", Journal of the Chinese Chemical Society, vol. 49, 2002, pp. 1041-1044.
Zhou, "The Synthesis and Characterization of 1-Benzyl-3-N-(Beta-D-glucoside-1-yl)-5-fluorouracil", Hecheng Huaxue, vol. 9, No. 3, 2001, pp. 272-274.

* cited by examiner

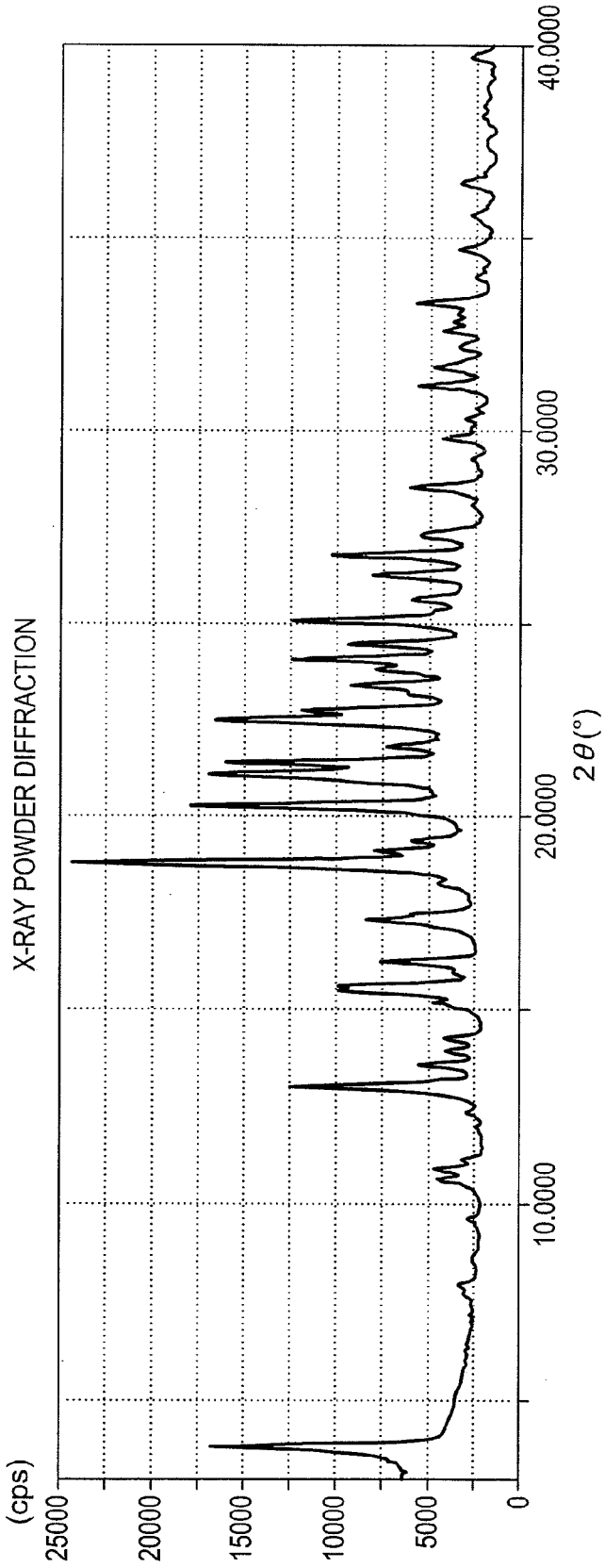

X-RAY POWDER DIFFRACTION
(cps)
25000
20000
15000
10000
5000
0
10.0000
20.0000
30.0000
40.0000
2θ(°)

FIG. 1

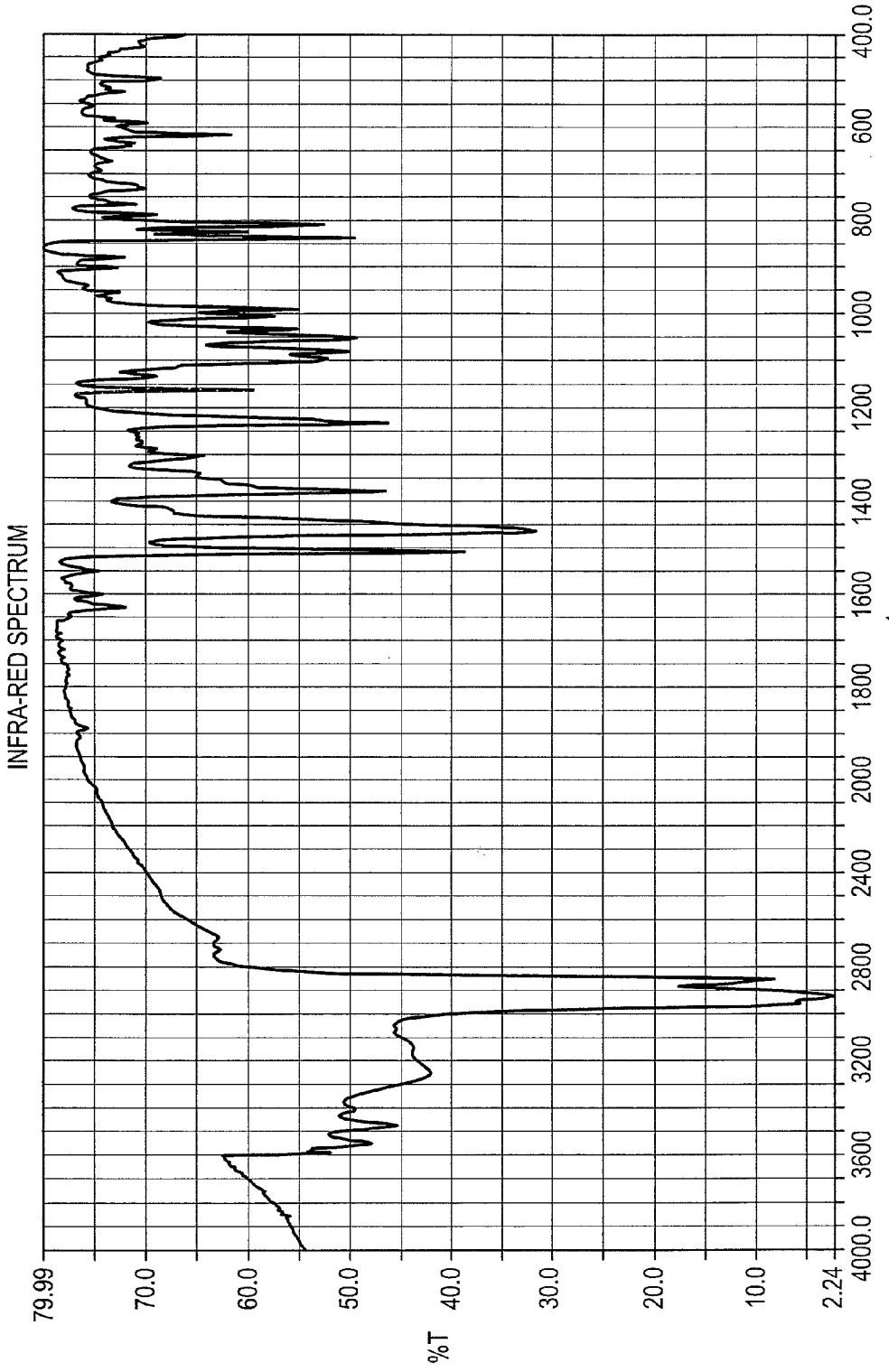

INFRA-RED SPECTRUM
%T
79.99
70.0
60.0
50.0
40.0
30.0
20.0
10.0
2.24
4000.0
3600
3200
2800
2400
2000
1800
1600
1400
1200
1000
800
600
400.0
cm-1

FIG.2

CRYSTALLINE FORM OF 1-(β-D-GLUCOPYRANOSYL)-4-METHYL-3-[5-(4-FLUOROPHENYL)-2-THIENYL-METHYL]BENZENE HEMIHYDRATE

This application is a Continuation of U.S. application Ser. No. 11/987,670 filed Dec. 3, 2007, which issued as U.S. Pat. No. 7,943,582 on May 17, 2011, which claims the benefit of priority under 35 U.S.C. §119(e) of U.S. Application No. 60/868,426, filed Dec. 4, 2006. U.S. application Ser. No. 11/987,670 also claims the benefit of priority of JP 2006-327019, filed Dec. 4, 2006. The entire content of each of the above-identified applications is hereby incorporated by reference.

BACKGROUND OF THE INVENTION

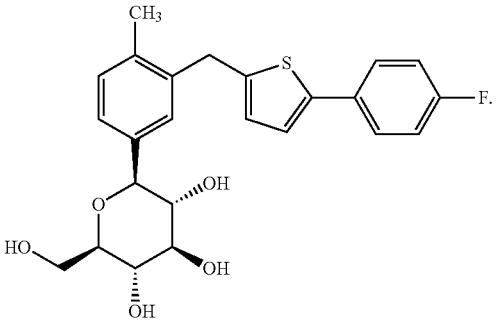
1. Field of the Invention

This invention relates to a crystalline form of 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene hemihydrate useful as an inhibitor of sodium-dependent glucose transporter, to methods for its preparation and isolation, to pharmaceutical compositions which include the compound and a pharmaceutically acceptable carrier, and to pharmaceutical methods of treatment.

2. Description of the Related Art

WO 2005/012326 pamphlet discloses a class of compounds that are inhibitors of sodium-dependent glucose transporter (SGLT) and thus of therapeutic use for treatment of diabetes, obesity, diabetic complications, and the like. There is described in WO 2005/012326 pamphlet 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene of formula (I):

(I)



In general, for commercial use it is important that a product should have good handling qualities. Additionally, there is a need to produce the product in a pure and crystalline form to enable formulations to meet exacting pharmaceutical requirements and specifications.

And it is desirable that the product should be in a form that is readily filterable and easily dried. Additionally, it is economically desirable that the product be stable for extended periods of time without the need for specialized storage conditions.

But there have been difficulties in obtaining a crystal form of the compound of formula (I) from organic solvents.

It has now been discovered that the compound of formula (I) hemihydrate can be produced in a crystalline form in a manner reproducible on a commercial scale.

SUMMARY OF THE INVENTION

The present invention provides a crystalline form of hemihydrate of the compound of formula (I) as a novel material, in particular in pharmaceutically acceptable form.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1**:

X-ray powder diffraction pattern of the crystalline of hemihydrate of the compound of formula (I).

FIG. **2**:

Infra-red spectrum of the crystalline of hemihydrate of the compound of formula (I).

DETAILED DESCRIPTION OF THE INVENTION

The inventors of the present invention have found that the compounds of formula (I) can be crystallized from a water-containing solvent and the crystalline form of hemihydrate of the compounds (I) have good handling qualities and characteristics.

Accordingly, the present invention is directed to:

1. A crystalline of hemihydrate of 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene.

2. A crystalline of hemihydrate of 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene characterized by a powder x-ray diffraction pattern comprising the following 2θ values measured using CuK_α radiation: 4.36±0.2, 13.54±0.2, 16.00±0.2, 19.32±0.2, 20.80±0.2.

3. A crystalline of hemihydrate of 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene, having substantially the same X-ray powder diffraction pattern as set out in FIG. **1**.

4. A crystalline of hemihydrate of 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene, having substantially the same IR spectrum, as set out in FIG. **2**.

5. A process for the preparation of a crystalline of hemihydrate of 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene, which comprises forming a solution of 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene and crystallizing said hemihydrate from the solution by precipitation or recrystallization.

6. A pharmaceutical composition comprising an effective amount of a crystalline of hemihydrate of 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl] benzene and a pharmaceutically acceptable carrier.

7. A method for treatment or delaying the progression or onset of diabetes mellitus, diabetic retinopathy, diabetic neuropathy, diabetic nephropathy, delayed wound healing, insulin resistance, hyperglycemia, hyperinsulinemia, elevated blood levels of fatty acids, elevated blood levels of glycerol, hyperlipidemia, obesity, hypertriglyceridemia, Syndrome X, diabetic complications, atherosclerosis, or hypertension, which comprises administering a therapeutically effective amount of a crystalline of hemihydrate of 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene.

As discussed, the present invention includes a certain solid state crystalline form. Several methods for characterizing such forms exist, and the invention should not be limited by the methods chosen or the instrumentation used in characterizing the compounds of the present invention. For example, with regard to x-ray diffraction patterns, the diffraction peak intensities in the experimental patterns can vary, as is known in the art, primarily due to preferred orientation (non-random

orientation of the crystals) in the prepared sample. As such, the scope of the present invention must be considered in light of the variability of characterization that is appreciated by those skilled in the art.

X-Ray Powder Diffraction

The crystalline form of the present invention (I) is characterized by its X-ray powder diffraction pattern. The X-ray diffraction pattern of the crystalline of hemihydrate of the compound (I) was measured on an X-ray diffractometer (RINT-TTR III, Rigaku, Tokyo, Japan) with measured using $CuK_{\square}$ radiation. Methodology of X-ray powder diffraction is as follows:

Scanning rate: 2.00 degree/minute.

Target: $CuK_{\square}$.

Voltage: 50 kV.

Current: 300 mA.

Scan range: from 3 to 40.0 degree.

Sampling width: 0.0200 degree.

Infra-Red Spectrum

The infra-red spectrum of the crystalline form of the present invention in mineral oil comprises the following main peaks: 1626, 1600, 1549, and 1507 cm^{-1}.

The infra-red spectrum of crystalline compound (I) hemihydrate is shown in the accompanying drawing in which the ordinate is the transmittance in % and the abscissa is the wavenumber in cm^{-1}.

Thermogravimetric Analysis

The crystalline form of the present invention has been observed to exist in a hemihydrate form. The theoretical water content of the crystalline of the present invention is 1.98%. The thermogravimetric analysis for the crystalline of the present invention shows a mass loss of 1.705%.

Methodology of thermogravimetric analysis is as follows: about 8 mg of compound (I) hemihydrate is weighed and transferred in an aluminum cell holder for TG-50 (Shimadzu, Japan), and then, the thermogravimetric (TG) thermal curve of crystalline compound (I) hemihydrate is determined at a heat rate of 5° C./minute. Typical measuring range is from ambient to 150° C.

The present invention also provides a process for producing the crystalline form of hemihydrate of the compound (I) which comprises forming a solution of compound (I) and precipitating the crystalline form from solution.

Typically, the crystalline of hemihydrate of the compound (I) may be obtained from a mixture of the compound of formula (I), a good solvent and water, optionally containing a poor solvent.

Sometimes some impurities may act as crystallization inhibitors, and impurities need to be removed using a conventional manner, such as silica gel column chromatography. However, the crystalline of hemihydrate of the compound of formula (I) can even be obtained from relatively impure compound (I).

The present invention also provides a pharmaceutical composition comprising the crystalline of hemihydrate of the compound (I) and a pharmaceutically acceptable carrier.

The crystalline compound of the present invention possesses activity as inhibitors of sodium-dependent glucose transporters, and show excellent blood glucose lowering effect.

The crystalline form of the present invention are expected to be useful in the treatment, prevention or delaying the progression or onset of diabetes mellitus (type 1 and type 2 diabetes mellitus, etc.), diabetic complications (such as diabetic retinopathy, diabetic neuropathy, diabetic nephropathy), postprandial hyperglycemia, delayed wound healing, insulin resistance, hyperglycemia, hyperinsulinemia, elevated blood levels of fatty acids, elevated blood levels of glycerol, hyperlipidemia, obesity, hypertriglyceridemia, Syndrome X, atherosclerosis, or hypertension.

The crystalline form of the present invention or a pharmaceutically acceptable salt thereof may be administered either orally or parenterally, and can be used in the form of a suitable pharmaceutical preparation. Suitable pharmaceutical preparations for oral administration include, for example, solid preparations such as tablets, granules, capsules, and powders, or solution preparations, suspension preparations, emulsion preparations, and the like. Suitable pharmaceutical preparations for parenteral administration include, for example, suppositories; injection preparations or intravenous drip preparations, using distilled water for injection, physiological saline solution or aqueous glucose solution; and inhalant preparations.

The pharmaceutical compositions herein will contain, per dosage unit, e.g., tablet, capsule, powder, injection, suppository, teaspoonful and the like, from about 0.01 mg/kg to about 100 mg/kg body weight (preferably from about 0.01 mg/kg to about 50 mg/kg; and, more preferably, from about 0.01 mg/kg to about 30 mg/kg) of the active ingredient, and may be given at a dosage of from about 0.01 mg/kg/day to about 100 mg/kg/day (preferably from about 0.01 mg/kg/day to about 50 mg/kg/day and more preferably from about 0.01 mg/kg/day to about 30 mg/kg/day). The method of treating a disorder described in the present invention may also be carried out using a pharmaceutical composition comprising the crystalline form as defined herein and a pharmaceutical acceptable carrier. The dosage form will contain from about 0.01 mg/kg to about 100 mg/kg (preferably from about 0.01 mg/kg to about 50 mg/kg; and, more preferably, from about 0.01 mg/kg to about 30 mg/kg) of the active ingredient, and may be constituted into any form suitable for the mode of administration selected. The dosages, however, may be varied depending upon administration routes, the requirement of the subjects, the severity of the condition being treated and the compound being employed. The use of either daily administration or post-periodic dosing may be employed.

The crystalline form of the present invention may be used, if necessary, in combination with one or more of other antidiabetic agents, antihyperglycemic agents and/or agents for treatment of other diseases. The present compounds and these other agents may be administered in the same dosage form, or in a separate oral dosage form or by injection.

The dosage of those agents may vary according to, for example, ages, body weight, conditions of patients, administration routes, and dosage forms.

These pharmaceutical compositions may be orally administered to mammalian species including human beings, apes, and dogs, in the dosage form of, for example, tablet, capsule, granule or powder, or parenterally administered in the form of injection preparation, or intranasally, or in the form of transdermal patch.

The crystalline form of hemihydrate of the compound of formula (I) can be prepared from a mixture of the compound (I), a good solvent and water, optionally containing a poor solvent.

Examples of good solvents which have been found suitable include ketones (e.g., acetone, 2-butanone), esters (e.g., ethyl acetate, methyl acetate), alcohols (e.g., methanol, ethanol, i-propanol), and a mixture of these solvents. Examples of poor solvents include alkanes (e.g., hexane, heptane), aromatic hydrocarbons (e.g., benzene, toluene), ethers (e.g., diethyl ether, dimethyl ether, diisopropyl ether) and a mixture of these solvents.

One preferred preparation of the crystalline form of hemihydrate of the compound of formula (I) typically involves dissolving in a good solvent (e.g., ketones or esters) crude or amorphous compound of formula (I) prepared in accordance with the procedures described in WO 2005/012326 pamphlet, and adding water and a poor solvent (e.g., alkanes or ethers) to the resulting solution, followed by filtration.

In case that a good solvent is soluble in water, a poor solvent needs not be used and water may be added to the solution of the compound of formula (I) in the good solvent so the solubility of the compound of formula (I) can be decreased in the solution.

In case that a poor solvent is used, water is preferably used in amount of 1 to 10 molar equivalents to the compound of formula (I), the good solvent is preferably used in amount of 10 to 100 times of volume of water, and the poor solvent is preferably used in amount of 0.1 to 10 times of volume of the good solvent.

The precise conditions under which the crystalline of hemihydrate of the compound (I) is formed may be empirically determined.

Under these conditions, crystallization can preferably be carried out at a lowered, ambient or elevated temperature.

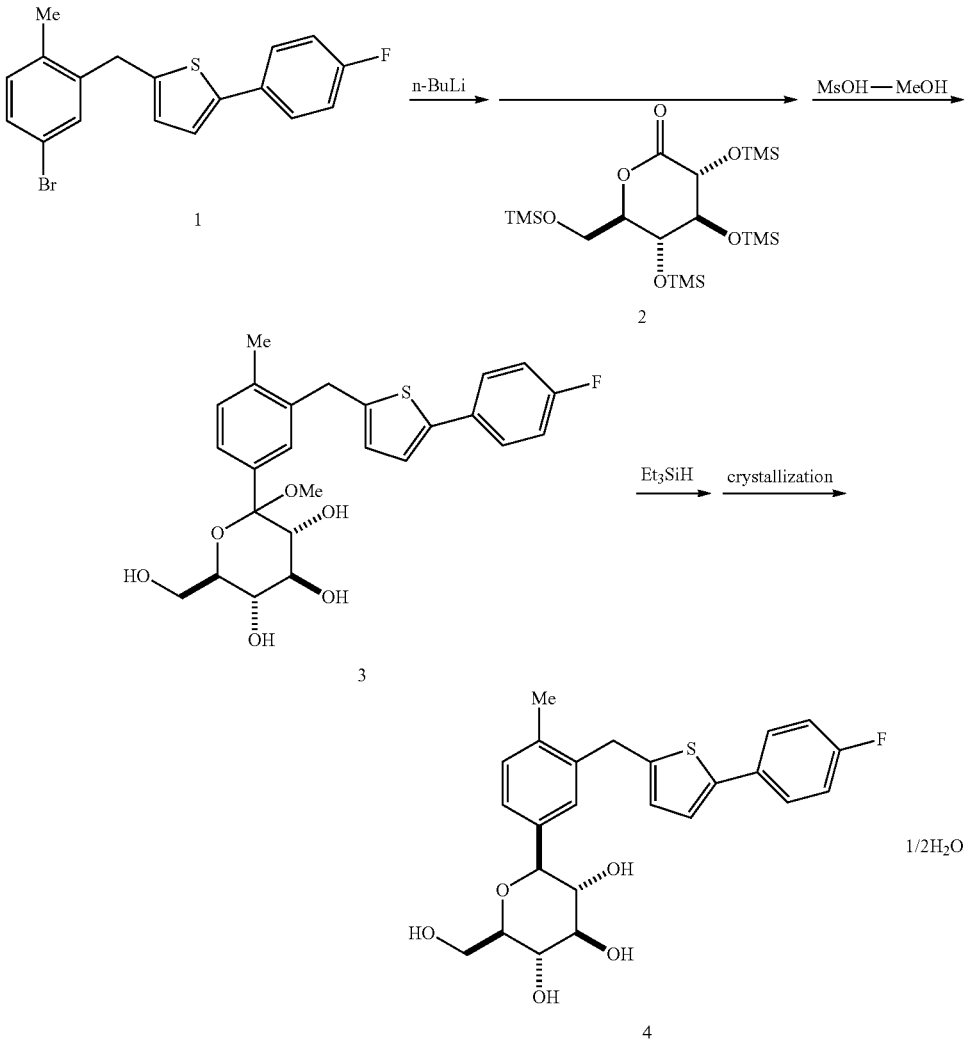
The crystalline form of hemihydrate of the compound of formula (I) is significantly easier to isolate than amorphous form of the compound and can be filtered from the crystallization medium after cooling, and washed and dried. Also, the crystalline form of the present invention is more stable than the amorphous form of the compound of formula (I).

EXAMPLES

Example 1

Crystalline 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene hemihydrate

1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene was prepared in a similar manner as described in WO 2005/012326.



(1) To a solution of 5-bromo-1-[5-(4-fluorophenyl)-2-thienylmethyl]-2-methylbenzene (1, 28.9 g) in tetrahydrofuran (480 ml) and toluene (480 ml) was added n-butyllithium (1.6M hexane solution, 50.0 ml) dropwise at −67 to −70° C. under argon atmosphere, and the mixture was stirred for 20

minutes at the same temperature. Thereto was added a solution of 2 (34.0 g) in toluene (240 ml) dropwise at the same temperature, and the mixture was further stirred for 1 hour at the same temperature. Subsequently, thereto was added a solution of methanesulfonic acid (21.0 g) in methanol (480 ml) dropwise, and the resulting mixture was allowed to warm to room temperature and stirred for 17 hours. The mixture was cooled under ice—water cooling, and thereto was added a saturated aqueous sodium hydrogen carbonate solution. The mixture was extracted with ethyl acetate, and the combined organic layer was washed with brine and dried over magnesium sulfate. The insoluble was filtered off and the solvent was evaporated under reduced pressure. The residue was triturated with toluene (100 ml)—hexane (400 ml) to give 1-(1-methoxyglucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]-benzene (3) (31.6 g). APCI-Mass m/Z 492 ($M+NH_4$).

(2) A solution of 3 (63.1 g) and triethylsilane (46.4 g) in dichloromethane (660 ml) was cooled by dry ice—acetone bath under argon atmosphere, and thereto was added dropwise boron trifluoride.ethyl ether complex (50.0 ml), and the mixture was stirred at the same temperature. The mixture was allowed to warm to 0° C. and stirred for 2 hours. At the same temperature, a saturated aqueous sodium hydrogen carbonate solution (800 ml) was added, and the mixture was stirred for 30 minutes. The organic solvent was evaporated under reduced pressure, and the residue was poured into water and extracted with ethyl acetate twice. The organic layer was washed with water twice, dried over magnesium sulfate and treated with activated carbon. The insoluble was filtered off and the solvent was evaporated under reduced pressure. The residue was dissolved in ethyl acetate (300 ml), and thereto were added diethyl ether (600 ml) and H_2O (6 ml). The mixture was stirred at room temperature overnight, and the precipitate was collected, washed with ethyl acetate—diethyl ether (1:4) and dried under reduced pressure at room temperature to give 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene hemihydrate (33.5 g) as colorless crystals. mp 98-100° C. APCI-Mass m/Z 462 ($M+NH_4$). ^{1}H-NMR (DMSO-d_6) δ 2.26 (3H, s), 3.13-3.28 (4H, m), 3.44 (1H, m), 3.69 (1H, m), 3.96 (1H, d, J=9.3 Hz), 4.10, 4.15 (each 1H, d, J=16.0 Hz), 4.43 (1H, t, J=5.8 Hz), 4.72 (1H, d, J=5.6 Hz), 4.92 (2H, d, J=4.8 Hz), 6.80 (1H, d, J=3.5 Hz), 7.11-7.15 (2H, m), 7.18-7.25 (3H, m), 7.28 (1H, d, J=3.5 Hz), 7.59 (2H, dd, J=8.8, 5.4 Hz). Anal. Calcd. for $C_{24}H_{25}FO_5S.0.5H_2O$: C, 63.56; H, 5.78; F, 4.19; S, 7.07. Found: C, 63.52; H, 5.72; F, 4.08; S, 7.00.

Example 2

An amorphous powder of 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene (1.62 g) was dissolved in acetone (15 ml), and thereto were added H_2O (30 ml) and a crystalline seed. The mixture was stirred at room temperature for 18 hours, and the precipitate was collected, washed with acetone—H_2O (1:4, 30 ml) and dried under reduced pressure at room temperature to give 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene hemihydrate (1.52 g) as colorless crystals. mp 97-100° C.

The invention claimed is:

1. A crystalline form of 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene hemihydrate having an infra-red spectrum in mineral oil comprising the following main peaks: 1626, 1600, 1549, and 1507 cm^{-1}.

2. A process for the preparation of a crystalline form of 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene hemihydrate of claim **1**, which comprises forming a solution of 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluoro-phenyl)-2-thienylmethyl]benzene and crystallizing said hemihydrate from the solution by precipitation or recrystallization.

3. A pharmaceutical composition comprising an effective amount of a crystalline form of 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene hemihydrate of claim **1** and a pharmaceutically acceptable carrier.

4. A method for treatment or delaying the progression or onset of diabetes mellitus, diabetic retinopathy, diabetic neuropathy, diabetic nephropathy, delayed wound healing, insulin resistance, hyperglycemia, hyperinsulinemia, elevated blood levels of fatty acids, elevated blood levels of glycerol, hyperlipidemia, obesity, hypertriglyceridemia, Syndrome X, diabetic complications, atherosclerosis, or hypertension, which comprises administering a therapeutically effective amount of a crystalline form of 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene hemihydrate of claim **1** to a subject in need thereof.

5. A method for inhibiting a sodium-dependent glucose transporter in a mammal in need thereof, comprising administering to said mammal a therapeutically effective amount of the crystalline form of hemihydrate of 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene of claim **1**.

* * * * *